Biohaven Pharmaceuticals

Protocol BHV3500-201

BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine

Statistical Analysis Plan

Version 2.0

Date: 15-November-2019

SIGNATURE PAGE

Protocol Title:	BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine
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Author:	PPD PPD Cytel Inc.
	Signature:_____
	Date:_____

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 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 PPD PPD Biohaven Pharmaceuticals	Signature:_____
	Date:_____
PPD PPD PPD Biohaven Pharmaceuticals	Signature:_____
	Date:_____

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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
BUN	Blood urine nitrogen
CI	Confidence interval
CPK	Creatinine phosphokinase
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Technical Criteria for Adverse Events
CV	Cardiovascular
DAIDS	Division of Acquired Immune Deficiency Syndrome
ECG	Electrocardiogram
eDiary	Electronic diary
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
eGFR	Estimated glomerular filtration rate
FCS	Fully conditional method
FDS	Functional Disability Scale
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
MBS	Most bothersome symptom
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MQoLQ	Migraine Specific Quality of Life Questionnaire
NC=F	Non-Completer = Failure

Abbreviation	Definition
NC1=F	Non-Completer With Missing Data at More Than 1 Time Point = Failure
NC=M	Non-Completer = Missing
NRS	Numeric rating scale
PID	Patient identifier
PoM	Preference of medication
PT	Preferred term
RM=F	Rescue Medication = Failure
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SDS	Sheehan Disability Scale
SOC	System organ class
TBL	Total bilirubin
ULN	Upper limit of normal
WHO-DD	World Health Organization-Drug Dictionary

REVISION HISTORY

Version	Description of Change
1.0	Original Issue
2.0	• Added a revision history section. • Abbreviations: Removed ATC. • Section 6.2.3: Modified the list of significant protocol deviations. • Section 6.2.4.1: Added childbearing potential for females to the table of demographics and baseline characteristics. • Section 6.2.4.3: Specified that if the last migraine date is missing, then it will be imputed with the informed consent date. • Section 6.2.4.6: Modified contents of the 3 x 3 cross-tabulation of historical MBS versus MBS at on-study migraine attack onset. • Section 6.2.5.2: Replaced ATC with therapeutic class. Specified that rescue medication dates will not be imputed, and that rescue medication times will not be imputed, unless specified otherwise. • Section 6.3: Changed “95%” to “98.3” and “risk” to “percentage” throughout section. Specified that treatment comparisons of binary endpoints will be stratified by prophylactic migraine medication use at randomization except within subgroups. • Section 6.3.3.1: Added a table of pain freedom outcomes by subgroups. Removed “stratified” from overall percentages by treatment group. Specified that the principal analysis will be repeated unstratified for each subgroup level. • Section 6.3.3.2: Added a table of MBS freedom outcomes by subgroups. Specified that the principal analysis will be repeated unstratified for each subgroup level. • Section 6.3.4.3: Specified that analyses will be based on evaluable mITT subjects, i.e., mITT subjects with rescue medication start date on or before the study drug start date + 1 day and missing rescue medication start time will be excluded. • Section 6.3.4.5 through 6.3.4.8, 6.3.5.2: Specified that subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the specified hierarchy for an endpoint will be chosen. • Section 6.3.4.9: Specified that subjects who meet more than 1 relapse criterion will be classified according to the first relapse criterion met; in case of ties, the first relapse subcategory that is met in the specified hierarchy will be chosen. • Section 6.3.4.10: Removed “stratified” from overall percentages by treatment group. • Section 6.3.5.2: Added a KM table, KM plot and time-to-event distribution table for the following endpoints: pain freedom through 4 hours post-dose; MBS freedom through 8 hours post-dose for subjects with MBS reported at on-study migraine attack onset. Modified time-to-event algorithm to include imputed rescue medication start date/time. • Section 6.5.2: Specified that LDL cholesterol and triglycerides will be assessed by fasting status rather than by 8-hour fasting status. Specified that the by-subject listing of LFT values and ratios to ULN will display all results over time for enrolled subjects with select LFT elevations (ALT or AST > 3 x ULN; ALP or TBL > 2 x ULN) at any time point. • Section 6.5.1.3: Removed the table of AEs leading to death. • Section 7.1.1.1: Specified that CI levels will be 98.3% for efficacy endpoints and 95% for all other endpoints.

Version	Description of Change
	• Section 7.3: Modified the definition of study drug start date/time to also use data from the eDiary Study Medication Intake Report. Added imputed rescue medication start date/time, and specified that it will be used only for time-to-event efficacy analyses in Section 6.3.5.2, and not for time to rescue medication use analyses in Section 6.3.4.3. • Section 7.6.3.1: Specified that subjects who took study medication without using the eDiary will have the study medication date and time reported by the site on the eDiary Study Medication Intake Report.

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine.

This SAP is based on the BHV3500-201, V4.0, protocol dated 08-August-2019. 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 BHV-3500 compared with placebo in the acute treatment of migraine as measured by the co-primary endpoints of **pain freedom** and **freedom from the most bothersome symptom** (MBS), associated with migraine, at 2 hours post dose, while identifying an optimal dose to support the Phase 3 clinical trials.

1.2.2 Secondary Objectives

The secondary objectives are:

- To evaluate BHV-3500 compared to placebo on pain relief at 2 hours post-dose.
- To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 2 hours post-dose according to the Functional Disability scale.
- To evaluate BHV-3500 compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
- To evaluate BHV-3500 compared to placebo on freedom from photophobia at 2 hours post-dose.
- To evaluate BHV-3500 compared to placebo on freedom from phonophobia at 2 hours post-dose.
- To evaluate BHV-3500 compared to placebo on pain relief at 60 minutes post-dose.
- To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 60 minutes post-dose according to the Functional Disability scale.
- To evaluate BHV-3500 compared to placebo on pain relief at 30 minutes post-dose.
- To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 30 minutes post-dose according to the Functional Disability scale.

- To evaluate BHV-3500 compared to placebo on sustained pain relief from 2 to 24 hours post-dose.
- To evaluate BHV-3500 compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.
- To evaluate BHV-3500 compared to placebo on sustained pain relief from 2 to 48 hours post-dose.
- To evaluate BHV-3500 compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.
- To evaluate BHV-3500 compared to placebo on freedom from nausea at 2 hours post-dose.
- To evaluate BHV-3500 compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose.

1.2.3 Exploratory Objectives

The exploratory objectives are:

- To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 24 hours post dose according to the Functional Disability scale.
- To evaluate the effect of BHV-3500 relative to placebo on the Migraine Preference of Medication (PoM).
- To evaluate BHV-3500 relative to placebo for pain freedom at all scheduled time points post dose.
- To evaluate BHV-3500 relative to placebo for pain relief at all scheduled time points post dose.
- To evaluate BHV-3500 relative to placebo for freedom from MBS at all scheduled time points post dose.
- To evaluate BHV-3500 relative to placebo for freedom from functional disability at all scheduled time points post dose.
- To evaluate the effect of BHV-3500 relative to placebo on the Migraine Quality of Life Questionnaire (MQoLQ).
- To evaluate the tolerability and safety of BHV-3500 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 BHV-3500 relative to placebo on the Sheehan Suicidality Tracking Scale (S-STS).

2 STUDY DESIGN

2.1 Synopsis of Study Design

BHV3500-201 is a Phase II, double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of BHV-3500 as compared to placebo in the treatment of moderate or severe migraine.

The design of the study is illustrated in Figure 1. As shown in the figure, after providing informed consent, subjects will first participate in the screening phase (3-28 day period) to determine eligibility for the study. Approximately 1,900 subjects will be screened to randomize approximately 1,600 subjects to study medication (BHV-3500 5 mg, BHV-3500 10 mg, BHV-3500 20 mg, or matching placebo).

After randomization, study medication will be dispensed to subjects to take home for up to 45 days. Subjects will be dispensed one Aptar Unit Dose System (UDS) liquid spray device containing a single dose of study medication BHV-3500 or a matching placebo. The 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 also record efficacy data and outcomes research measures in their eDiary.

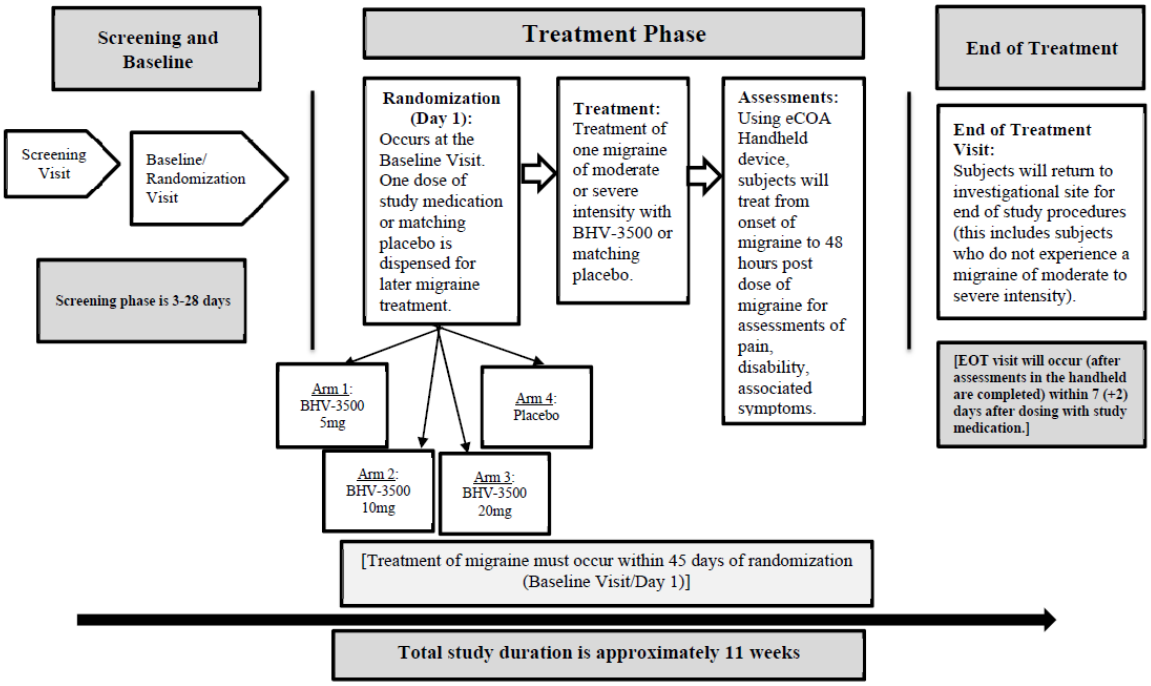
Subjects will return to the study site within 7 days of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety. If a subject has NOT experienced a migraine headache of sufficient severity within 45 days after randomization, they still are required to complete all EOT visit procedures and return unused study medication and eDiary to the investigational site.

2.2 Randomization Methodology

Per protocol, subjects in this study may be randomized only once.

The study will randomize approximately 1,600 subjects. The subjects will be randomized in a 1:1:1:1 ratio across 4 treatment groups (BHV-3500 5 mg, BHV-3500 10 mg, BHV-3500 20 mg, or placebo); see Figure 1. The randomization will be stratified by prophylactic migraine medication use (yes or no).

Figure 1: Study Schematic



2.3 Objective Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The four attributes of an estimand include the population of interest, endpoint of interest, specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the endpoint.

For all objectives, the population of interest is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval. Refer to the protocol for inclusion/exclusion criteria.

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation. Rescue medication taken at or before the time point of interest defining the endpoint will be considered an intercurrent event. This event is relevant to all efficacy endpoints, except the secondary endpoint of rescue medication use within 24 hours post-dose.

For efficacy objectives, intercurrent events will be handled with a composite strategy, i.e., the occurrence of the intercurrent event will be integrated as a component of the endpoint. See Section 6.3.1 for additional details.

For safety and outcomes research objectives, intercurrent events will be handled with a treatment policy strategy, i.e., the occurrence of the intercurrent event will be considered irrelevant, such that all observed values of the endpoint of interest will be used regardless of rescue medication use.

2.3.1 Primary Objective Estimands

Both co-primary objectives have efficacy endpoints. The estimands corresponding to the co-primary objectives are shown in Table 1.

For each objective, intercurrent events will be handled with a composite strategy described in Section 2.3. The population summary is the difference in the percentage of subjects achieving the endpoint between each BHV-3500 treatment group (5 mg, 10 mg, 20 mg) and the Placebo treatment group.

Table 1: Co-Primary Objective Estimands

Objective	**Pain Freedom at 2 hours post-dose**
Endpoint	Percentage of subjects with no pain at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose
Objective	**MBS Freedom at 2 hours post-dose**
Endpoint	Percentage of subjects with (1) MBS reported at on-study migraine onset before taking study drug, (2) MBS absent at 2 hours post-dose, (3) and no intervening rescue medication taken at or before 2 hours post-dose

2.3.2 Secondary Objective Estimands

All secondary objectives have efficacy endpoints. The estimands corresponding to the secondary objectives are shown in Table 2.

For each objective, intercurrent events are handled with a composite strategy described in Section 2.3, unless specified otherwise. The population summary is the difference in the percentage of subjects achieving the endpoint between each BHV-3500 treatment group (5 mg, 10 mg, 20 mg) and the Placebo treatment group.

Table 2: Secondary Objective Estimands

Objective	**Pain Relief at 30 minutes, 60 minutes, and 2 hours post-dose**
Endpoint	Percentage of subjects with mild or no pain at the specified time point and no intervening rescue medication taken at or before the specified time point
Objective	**Return to Normal Function at 30 minutes, 60 minutes, and 2 hours post-dose**
Endpoint	Percentage of subjects with normal function at the specified time point and no intervening rescue medication taken at or before the specified time point; evaluated for subjects with functional disability at on-study migraine attack onset
Objective	**Probability of Rescue Medication within 24 hours post-dose**
Endpoint	Percentage of subjects taking rescue medication within 24 hours post-dose
Intercurrent Events	Not applicable (intercurrent event is the endpoint)
Objective	**Photophobia Freedom at 2 hours post-dose**
Endpoint	Percentage of subjects with photophobia absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose; evaluated for subjects with photophobia present at on-study migraine attack onset
Objective	**Phonophobia Freedom at 2 hours post-dose**
Endpoint	Percentage of subjects with phonophobia absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose; evaluated for subjects with phonophobia present at on-study migraine attack onset
Objective	**Sustained Pain Relief from 2 to 24 hours post-dose, and 2 to 48 hours post-dose**
Endpoint	Percentage of subjects with (1) mild or no pain from the start to the end of the time period of interest, (2) missing pain data at ≤ 1 time point from 3 to 8 hours post-dose, and (3) no intervening rescue medication taken at or before the end of the time period of interest
Objective	**Sustained Pain Freedom from 2 to 24 hours post-dose, and from 2 to 48 hours post-dose**
Endpoint	Percentage of subjects with (1) no pain from the start to the end of the time period of interest, (2) missing pain data at ≤ 1 time point from 3 to 8 hours post-dose, and (3) no intervening rescue medication taken at or before the end of the time period of interest
Objective	**Nausea Freedom at 2 hours post-dose**
Endpoint	Percentage of subjects with nausea absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose; evaluated for subjects with nausea present at on-study migraine attack onset
Objective	**Pain Relapse from 2 to 48 hours post-dose**
Endpoint	Percentage of subjects with (1) mild, moderate, or severe pain at any time point after 2 hours post-dose (2) missing pain data at ≤ 1 time point after 2 hours post-dose, and (3) no intervening rescue medication taken at or before 48 hours post-dose; evaluated for subjects with pain freedom at 2 hours post-dose

2.3.3 Exploratory Objective Estimands

Exploratory objectives have efficacy, safety, and outcomes research endpoints. The estimands corresponding to the exploratory objectives are shown in Table 3.

Table 3: Exploratory Objective Estimands

Objective	**Return to Normal Function at 24 hours post-dose – Efficacy**
Endpoint	Percentage of subjects with normal function at 24 hours post-dose and no intervening rescue medication taken at or before 24 hours post-dose; evaluated for subjects with functional disability at on-study migraine attack onset
Intercurrent Events	Composite strategy: Intercurrent event captured in endpoint definition
Pop. Summary	Percentage of subjects by treatment group
Objective	**Preference of Medication (PoM) – Outcomes Research**
Endpoint	Percentage of subjects who prefer study medication to previous migraine medications; evaluated for those with PoM data
Intercurrent Events	Treatment policy strategy: No accounting for intercurrent events
Pop. Summary	Percentage of subjects by treatment group
Objectives	**Pain Freedom at all time points post-dose – Efficacy**
Population	mITT
Endpoint	Percentage of subjects with no pain at each time point post-dose and no intervening rescue medication taken at or before the time point
Intercurrent Events	Composite strategy: Intercurrent event captured in endpoint definition
Pop. Summary	Percentage of subjects by treatment group
Objectives	**Pain Relief at all time points post-dose – Efficacy**
Endpoint	Percentage of subjects with mild or no pain at each time point post-dose and no intervening rescue medication taken at or before the time point
Intercurrent Events	Composite strategy: Intercurrent event captured in endpoint definition
Pop. Summary	Percentage of subjects by treatment group
Objectives	**MBS Freedom at all time points post-dose – Efficacy**
Endpoint	Percentage of subjects with (1) MBS absent at each time point post-dose, (2) MBS reported at on-study migraine attack onset before study drug, and (3) no intervening rescue medication taken at or before the time point
Intercurrent Events	Composite strategy: Intercurrent event captured in endpoint definition
Pop. Summary	Percentage of subjects by treatment group
Objectives	**Return to Normal Function at all time points post-dose – Efficacy**
Endpoint	Percentage of subjects with normal function at each time point post-dose and no intervening rescue medication taken at or before the time point; evaluated for subjects with functional disability at on-study migraine attack onset
Intercurrent Events	Composite strategy: Intercurrent event captured in endpoint definition
Pop. Summary	Percentage of subjects by treatment group
Objectives	**Migraine Quality of Life Questionnaire (MQoL) – Outcomes Research**
Endpoint	Change from baseline in the total score at end of treatment visit
Intercurrent Events	Treatment policy strategy: No accounting for intercurrent events
Pop. Summary	Mean change from baseline in total score by treatment group
Objective	**Safety and Tolerability**
Endpoint	Frequency of adverse events (AEs) of at least moderate severity, serious adverse events (SAEs), and clinically relevant laboratory test abnormalities
Intercurrent Events	Treatment policy strategy: No accounting for intercurrent events
Pop. Summary	Number and percentage of subjects with safety events and findings
Objective	**Sheehan Suicidality Tracking Scale – Safety**
Endpoints	Change from baseline in the total score at end of treatment visit
Intercurrent Events	Treatment policy strategy: No accounting for intercurrent events
Pop. Summary	Percentage of subjects in each change from baseline category (< -1, -1, no change, 1, > 1) by treatment group

3 POPULATION SAMPLES FOR ANALYSES

The following population samples for analyses ("analysis sets") will be evaluated and used for presentation and analysis of the data:

- Enrolled subjects: Subjects who sign an informed consent form and are assigned a subject identification number, i.e., non-missing informed consent date.
- Randomized subjects: Enrolled subjects who receive a randomization treatment assignment from the interactive web response system (IWRS), i.e., non-missing IWRS randomization date.
- Treated subjects: Enrolled subjects who take study therapy (BHV-3500 or placebo), i.e., non-missing study drug start date/time.
- Modified Intent-to-Treat (mITT) subjects: Treated subjects who are randomized only once, have moderate to severe pain at on-study migraine attack onset, and have non-missing, post-baseline efficacy data (i.e., non-missing pain level, phonophobia status, photophobia status, nausea status, or functional disability level with finding date/time from the eDiary Post-Dose Migraine Report at any time point after the study drug start/time).

See Section 7.3 for derived dates.

4 SCHEDULE OF ANALYSES

All analyses described in this SAP will be performed after the last subject completes the end of treatment visit or discontinues from the study, and the database has been locked.

5 SAMPLE SIZE AND POWER

If 95% of the 400 subjects randomized to each treatment group treat a migraine on study, then there will be roughly 380 mITT subjects in each treatment group.

If the true response rates for pain freedom at 2 hours are 22% and 12% in the BHV-3500 and placebo groups, then a chi-square test at alpha=0.0167 will have 90% power. Similarly, if the true response rates for MBS freedom at 2 hours are 45% and 32% in the BHV-3500 and placebo groups, then a chi-square test at alpha=0.0167 will have 90% power. Under the assumption that the endpoints are independent, the power for both endpoints jointly is roughly 80%.

6 STATISTICAL METHODS

Tables will present results by treatment group (i.e., BHV-3500 5 mg, BHV-3500 10 mg, BHV-3500 20 mg, Placebo) and All BHV-3500 with the following exceptions:

- Results for enrolled subjects will be presented only by overall, without treatment group and All BHV-3500.
- Results for study population parameters (see Section 6.2) and pre-treatment safety will include overall, unless specified otherwise.
- Efficacy results for mITT subjects will be presented only by treatment group, without All BHV-3500 and overall.

The "All BHV-3500" treatment group will consist of subjects pooled across the three BHV-3500 treatment groups. Because this group is intended mainly to support safety, it will be included only in tables for the population samples of randomized subjects and treated subjects.

The population sample of treated subjects will be assessed by as-treated treatment group, i.e., by the treatment actually received, unless specified otherwise. Otherwise, all other population samples (i.e., randomized, mITT) will be assessed by as-randomized treatment group.

All statistical analyses will be performed using SAS statistical software (Version 9.4 or higher).

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Non-study medications will be coded using World Health Organization Drug Dictionary (WHO-DD). Refer to the latest version of Biohaven Dataset Guidelines for dictionary versions.

6.1 General Methods

6.1.1 Missing Data

For all binary efficacy endpoints, principal analyses will impute missing data as failure using methods described in Section 6.3.1 Sensitivity analysis of the co-primary endpoints will exclude subjects with missing data or impute missing data using different methods (see Section 6.3.3.1 and Section 6.3.3.2). Sensitivity analysis of exploratory efficacy endpoints will exclude subjects with missing data (see Section 6.3.5.2). Otherwise, all analyses will be based on observed data without using imputation.

6.1.2 Type I Error Control

Type I error will be controlled by a hierarchical gate-keeping procedure. First, the family of two co-primary endpoints will be tested. In particular, each BHV-3500 treatment group will be tested for superiority against placebo at a Bonferroni corrected alpha=0.0167 level for both co-primary endpoints. If both co-primary endpoint tests are determined to be significant for a BHV-3500 treatment group versus placebo, then the secondary endpoints will be tested for that BHV-3500 treatment group versus placebo using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at alpha=0.0167.

The secondary endpoints will be tested in the order shown in Section 1.2.2.

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.

6.1.3 Subgroups

For mITT subjects, the following efficacy subgroups are of interest:

- Age: < 40, ≥ 40 years
- Sex: female, male
- Race: White, Black or African American, Other including Asian, Asian
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Baseline body mass index (BMI; kg/m^2): < 25, ≥ 25 to < 30, ≥ 30
- Aura at on-study migraine attack onset: yes, no
- Historical number of moderate or severe migraine attacks per month: < median, ≥ median, where the median is calculated overall across treatment groups combined for mITT subjects and rounded to an integer.
- Triptan non-responder: yes, no (see Section 7.2).

Subgroup analyses will be performed for the co-primary efficacy endpoints only. Efficacy subgroup tables will present results by subgroup level for subjects with non-missing subgroup level data, unless specified otherwise.

Subgroup levels may be redefined or combined based on the availability of data.

6.2 Study Population

6.2.1 Population Samples for Analyses and Randomization

The number of subjects in each population sample for analysis described in Section 3 will be presented by as-randomized or as-treated treatment group, not randomized, and overall.

Inclusion and exclusion from the mITT population will be summarized by treatment group and overall as the number and percentage of randomized subjects in the following categories:

- Included in mITT population
- Excluded from mITT population
  - Treated
    - Pain level of mild, none, or not reported at on-study migraine attack onset
    - Randomized more than once
    - No post-baseline efficacy data (i.e., missing all of the following parameters from the eDiary Post-Dose Migraine Report after the study drug start date/time: pain level, nausea status, phonophobia status, photophobia status, and functional disability level)
  - Not treated.

A by-subject listing of population samples for analyses will be provided for enrolled subjects. The listing will flag subjects in population samples, and include as-treated treatment group only if different from as-randomized treatment group.

A by-subject listing of subjects excluded from the efficacy analysis will be provided for randomized subjects not in the mITT population sample, including the reason for exclusion (e.g., not treated). Treated subjects may have more than one exclusion reason.

A by-subject administrative listing of randomization scheme and codes will be provided for all randomization numbers and block numbers, even those not assigned to a subject. This listing will be sorted by randomization number and block number, and will contain the randomization number, site-subject ID, treatment group, randomization stratum, and randomization date.

6.2.2 Subject Disposition

Subject disposition will be based on the Study Exit Status case report form (CRF), unless noted otherwise.

Subject disposition from enrollment to randomization will be summarized for enrolled subjects by overall as the number and percentage of subjects in the following categories:

- Randomized
- Not randomized
    - Reasons for not completing the study, including not reported (e.g., adverse event, death). For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure will be also be included from the Inclusion/Exclusion Findings Summary CRF.

Subject disposition from randomization to treatment will be summarized for randomized subjects by as-randomized treatment group, All BHV-3500, and overall as the number and percentage of subjects in the following categories:

- Treated
- Not treated
    - Reasons for not completing the study, including not reported.

Subject disposition during the treatment phase will be summarized for treated subjects by as-treated treatment group, All BHV-3500, and overall as the number and percentage of subjects in the following categories:

- Completed study
- Did not complete study
    - Reasons for not completing the study, including not reported.

Subject disposition during the treatment phase will be summarized analogously for mITT subjects by as-randomized treatment group and overall to support efficacy.

The following by-subject listings will be provided for enrolled subjects: (1) subject disposition, including the informed consent date, randomization date, study drug start date/time, last contact date, and reason for not completing the study, if applicable; (2) eligibility with inclusion and exclusion criteria for all subjects, not just those who have non-missing criteria.

See Section 7.3 for derived dates.

6.2.3 Protocol Deviations

A significant protocol deviation is any deviation that could impact subject safety or the integrity of the trial, and are defined as follows:

- Informed Consent
- Inclusion Criteria (Specify criteria #)
- Exclusion Criteria (Specify criteria #)
- Concomitant Medication
- SAE Reporting
- Regulatory
- Drug Storage/ Preparation
- Drug Administration
- Visit Schedule
- ePRO Diary Noncompliance
- Noncompliance (i.e. trends, missed assessments)

The number and percentage of treated subjects with significant protocol deviations will be summarized by deviation type and by as-randomized treatment group, All BHV-3500, and overall. Deviation types will be presented in descending order of overall frequency.

A by-subject listing of significant protocol deviations will be provided for enrolled subjects.

6.2.4 Pre-Treatment Characteristics

Demographics and baseline characteristics, medical history, migraine history, cardiac and other risk factors, prior triptan response, and current triptan response, and migraine characteristics at on-study migraine attack onset will be summarized by as-randomized treatment group and overall for mITT subjects to support efficacy. These endpoints will also be summarized for treated subjects by as-treated treatment group, All BHV-3500, and overall to support safety.

In addition, demographics and baseline characteristics and migraine history will be summarized for (1) subjects enrolled but not randomized by overall only, and (2) subjects randomized but not in the mITT population by as-randomized treatment group, All BHV-3500, and overall.

Tables will display a “not reported” category for missing categorical variables, if applicable.

Prophylactic migraine medication use at randomization (yes, no) will be summarized by as-randomized treatment group, All BHV-3500, and overall for randomized subjects.

Baseline is defined according to population as follows:

- Enrolled subjects not randomized: Last non-missing value
- Randomized subjects not treated: Last non-missing value at or before the IWRS randomization date/time
- mITT subjects and treated subjects: Last non-missing value at or before the study drug start date/time (i.e., in the pre-treatment analysis period; see Sections 7.4 and 7.5).

The following by-subject listings of pre-treatment characteristics will be provided:

- Demographics, displaying informed consent date, birth date, age, sex, race, and ethnicity. All reported races will be displayed comma-concatenated alphabetically for subjects who reported multiple races (e.g., "Asian, White").
- Baseline characteristics (see Section 6.2.4.1).
- Medical history, displaying start date, stop date or ongoing, system organ class (SOC), preferred term (PT), and verbatim term.
- Migraine history split into general migraine history, migraine without aura symptom history, and migraine with aura symptom history.
- Cardiac and other risk factors for subjects with any risk factor present. Only records with "yes" responses to questions about having risk factors will be displayed.
- Prior triptan response, displaying triptan name, route, discontinuation reason, and symptom frequency.
- Current triptan response, displaying triptan name, route, and frequency of symptom relief.

6.2.4.1 Demographics and Baseline Characteristics

Demographics will include the following:

- Age (years) at informed consent calculated as: (informed consent date - birth date + 1) / 365.25 truncated to an integer, also categorized as < 40, ≥ 40, < 65, ≥ 65
- Sex (male, female)
- Childbearing potential, if female (yes, no)
- Race (White, Black or African American, other including Asian [i.e., American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, multiple]). Subjects with more than one race are counted only in the "multiple" category.
- Ethnicity (Hispanic or Latino, not Hispanic or Latino).

Baseline characteristics will include the following:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2), also categorized as < 25, ≥ 25 to < 30, ≥ 30
- Prophylactic migraine medication use at randomization (yes, no), i.e., IWRS randomization strata.

6.2.4.2 Medical History

Medical history will be summarized by SOC and PT, and displayed in descending order of overall frequency within SOC and PT.

6.2.4.3 Migraine History

Migraine history will include the following:

- Age (years) at migraine onset
- Time since last migraine (days) calculated as: (informed consent date – imputed last migraine date) for subjects with imputed last migraine date up to 1 year before informed consent date. Last migraine date will be imputed for partial dates using the same methodology as AE start dates, but using the informed consent date as the surrogate date (see Section 7.6.1.1 for AE start date imputation). If the last migraine date is missing, then it will be imputed with the informed consent date.
- Number of moderate to severe migraines per month, also categorized as < median and ≥ median (see Section 6.1.3)
- Average duration of untreated migraine attacks (hours)
- Primary migraine type (migraine without aura, migraine with aura)
- Most bothersome symptom (i.e., nausea, phonophobia, or photophobia)
- Migraine symptoms (i.e., headache attacks lasting 4-72 hours, unilateral location, pulsating quality, moderate or severe pain level, aggravation by or causing avoidance of routine physical activity, during headache: nausea and/or vomiting, during headache: photophobia and phonophobia)
- History of migraine without aura (yes, no)
- History of migraine with aura (yes, no). For subjects with a "yes" response to this question:
    - Aura symptoms (i.e., visual, sensory, speech and/or language, motor, brainstem, retinal)
    - Aura characteristics (i.e., at least one aura symptom spreads gradually over ≥ 5 min, and/or two or more symptoms occur in succession; each individual aura symptom lasts 5-60 min; at least one aura symptom is unilateral; the aura is accompanied, or followed within 60 min, by headache)

- Migraine with aura type (i.e., migraine with typical aura, typical aura with headache, and typical aura without headache).

6.2.4.4 Cardiac and Other Risk Factors

Cardiac and other risk factors will include the following:

- Any risk factor
- Ischemic coronary artery disease along with history of: angina pectoris; myocardial infarction; acute coronary syndrome; documented silent ischemia; percutaneous coronary intervention; history of stent placemen; coronary artery bypass surgery
- Other significant underlying cardiovascular (CV) disease (specify)
- Coronary artery vasospasm including Prinzmetal's angina
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders
- Other arrhythmias (specify)
- Stroke or transient ischemia attack
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Triptan hypersensitivity (specify)
- Treated for hypertension
- Diabetes
- Current smoker
- Treated with statins
- Family history of coronary artery disease.

6.2.4.5 Prior and Current Triptan Response

Prior triptan response will include historically discontinued triptan, route (e.g., intravenous, nasal), and reason for discontinuation (e.g., took too long to relieve headache pain) subcategorized as most or all of the time, some of the time, rarely, or never.

Current triptan response will include currently used triptan, route (e.g., intravenous, nasal), and durability of effect (e.g., freedom from pain within 2 hours, often satisfied with speed of pain relief) subcategorized as never, rarely, some of the time, most of the time, or all of the time.

6.2.4.6 Migraine Characteristics at On-Study Migraine Attack Onset

Characteristics at on-study migraine attack onset will include the following, and will be summarized only for mITT subjects:

- Pain level (none, mild, moderate, severe)
- MBS (nausea, phonophobia, photophobia)
- Nausea status (present, absent)
- Nausea level (none, mild, moderate, severe)
- Phonophobia status (present, absent)
- Phonophobia level (none, mild, moderate, severe)
- Photophobia status (present, absent)
- Photophobia level (none, mild, moderate, severe)
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura (yes, no).

See Section 7.6.3.2 for additional details.

An overall 3 x 3 cross-tabulation of the historical MBS (see Section 6.2.4.3) as rows, and the MBS at on-study migraine attack onset as columns will be presented for mITT subjects with non-missing paired MBS values. The number and percentage of subjects in the following row and column categories will be presented: nausea, phonophobia, photophobia, marginal total. In addition, the following statistics will be presented: asymmetric lambda value and 95% CI; symmetric lambda value and 95% CI; kappa coefficient value and 95% CI; and p-value from the chi-square test.

6.2.5 Exposure

6.2.5.1 Study Medication

Subjects report study drug exposure in the eDiary, whereas sites report study drug accountability on the Study Drug Accountability CRF.

eDiary study drug exposure will be summarized by as-randomized treatment group, All BHV-3500, and overall for randomized subjects, and will include the number and percentage of subjects in the following categories:

- Study drug taken (i.e., study drug start date/time not missing)
  - Study drug taken mistakenly before using eDiary (see Section 7.6.3.1)
  - Study drug actually received different from randomized treatment assignment (i.e., as-treated treatment group not equal to as-randomized treatment group).

- Study drug not taken (i.e., study drug start date/time missing).

Study drug accountability will be summarized by as-randomized treatment group, All BHV-3500, and overall for randomized subjects, and will include the number and percentage of subjects in the following categories:

- Kit dispensed and returned
  - Investigational product (IP) used
  - IP not used
  - IP use unknown or not reported (i.e., missing)
- Kit dispensed and not returned.

Two 2 x 2 cross-tabulations of eDiary study drug exposure and study drug accountability will be provided for randomized subjects by overall only. The number and percentage of subjects in each category will be summarized follows:

- Categories for study drug exposure in rows are "study drug taken" and "study drug not taken". Categories for study drug accountability in columns are "kit dispensed and returned" and "kit dispensed and not returned".
- Categories for study drug exposure in rows are "study drug taken" and "study drug not taken". Categories for study drug accountability in columns are "IP used" and "IP not used/unknown/not reported".

A by-subject listing of eDiary study drug exposure and study drug accountability will be provided for randomized subjects. Subjects for whom the eDiary study drug exposure and study drug accountability categories (as per cross-tabulations) do not match will be flagged.

6.2.5.2 Non-Study Medications

Non-study medications will be summarized by therapeutic class and preferred name in descending order of overall frequency. For each subject, multiple records of the same medication will be counted only once within each therapeutic class and preferred name. Imputed medication start and stop dates will be used to assign non-study medication type (prior or concomitant) to all non-study medications except rescue medications. See Section 7.6.2 for details on non-study medication start and stop date imputation, and definitions of non-study medication types.

The following non-study medications will be summarized by as-treated treatment group and All BHV-3500 for treated subjects:

- Prior medications, including results for overall treatment group: all; prophylactic migraine
- Current medications, including results for overall treatment group: all; prophylactic migraine
- Concomitant medications: all; prophylactic migraine
- Rescue medications.

Rescue medications will also be summarized by as-randomized treatment group for mITT subjects to support efficacy.

A by-subject listing of non-study medications will be provided by therapeutic class and preferred name for enrolled subjects. Prophylactic migraine and rescue medications will be identified, as well as medication type.

A by-subject listing of rescue medications will be provided by therapeutic class and preferred name for treated subjects.

Non-study medications will be identified from the Concomitant Medication and Rescue Medication CRFs.

Prophylactic migraine medications are defined as those with a "yes" response to the question about prophylactic migraine medication on the Concomitant Medication CRF.

Rescue medications are defined as non-study medications reported on the Rescue Medication CRF with complete medication dates, and either (1) medication date/time after the study drug start date/time, or (2) medication date at or after study drug start date if the medication time or study drug start time is missing. Rescue medication dates will not be imputed. Rescue medication times will not be imputed, unless specified otherwise (see Section 6.3.5.2).

6.3 Efficacy

Efficacy analyses will be based on mITT subjects by as-randomized treatment group only (excluding All BHV-3500 and overall).

Treatment comparisons of binary endpoints will be stratified by prophylactic migraine medication use at randomization except within subgroups. If a single cell has sparse data (< 5 subjects), then the analysis will be performed pooled across strata.

All CIs will be two-sided. In treatment comparisons of binary endpoints, CIs will be based on a normal approximation to the binomial distribution using asymptotic standard error (ASE). In descriptive analyses of binary endpoints, exact Clopper-Pearson CIs will be used. Otherwise, CIs for continuous endpoints will be based on the normal distribution.

A by-subject listing of eDiary migraine characteristics will be provided for randomized subjects that displays parameters listed in Section 7.6.3.2 at migraine attack onset and over time post-dose. The rescue medication start date/time and time to rescue medication use in hours will also be included (see Sections 6.3.4.3 and 7.3); data collected on or after the rescue medication start date/time will be flagged.

Post-dose efficacy data will be slotted into analysis windows automatically by the eDiary (see Section 7.6.3.2). All efficacy endpoints will be assessed using analysis windows, unless specified otherwise.

6.3.1 Principal Analysis Methods of Handling Missing Data and Intercurrent Events

Methods of handling missing data in principal analyses of binary efficacy endpoints are defined as follows:

- Non-Completer = Failure (NC=F): Subjects with missing data at a single time point will be classified as failures. This missing data imputation method will be applied to endpoints based on data from a single time point (e.g., co-primary endpoints at 2 hours post-dose).
- Non-Completer With Missing Data at More Than 1 Time Point = Failure (NC1=F): Subjects with missing data at > 1 time point post-dose in a specified time period will be classified as failures. This missing data imputation method will be applied to endpoints that are based on data from multiple time points (e.g., secondary endpoint of sustained pain freedom from 2 to 24 hours post-dose).
- Non-Completer = Missing (NC=M): Subjects with missing data at a single time point will be excluded from the analysis. This missing data exclusion method will be applied to endpoints based on data from a single time point (e.g., co-primary endpoints at 2 hours post-dose).

The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication will be classified as failures for all efficacy evaluations that are reported at or after taking rescue medication, i.e., (1) rescue medication start date/time ≤ eDiary finding date/time if start time is not missing, or (2) rescue medication start date ≤ eDiary finding date if start time is missing; see Sections 6.2.5.2 and 7.3). This method will apply to all efficacy analyses, except the secondary endpoint of rescue medication use within 24 hours post-dose.

6.3.2 Missing Efficacy Data

Missing efficacy data will be summarized by treatment group as the number and percentage of mITT subjects in the following categories:

- Missing pain data at each time point from 15 minutes through 48 hours post-dose. These categories are not mutually exclusive because subjects may have missing data at multiple time points.
- Number of time points with missing pain data from 2 hours to 48 hours post-dose: 0 (i.e., no missing pain data), 1, 2, 3, 4, 5, 6, 7. These categories are mutually exclusive.
- Missing data for the following efficacy parameters at 2, 24, and 48 hours post-dose: pain level, nausea status, phonophobia status, photophobia status, and functional disability level.

In addition, missing pain data at 2 hours post-dose will be summarized by subgroup level for each treatment group and overall for all subgroups specified in Section 6.1.3 plus the following subgroups:

- Pain level at on-study migraine attack onset (moderate or severe)
- MBS at on-study migraine attack onset (nausea, phonophobia, or photophobia)
- Rescue medication use: yes, no.

6.3.3 Primary Efficacy Endpoints

Both co-primary efficacy endpoints will be evaluated for mITT subjects.

A by-subject listing of pain freedom and MBS freedom outcomes at each post-dose time point will be provided for randomized subjects that includes prophylactic migraine medication use at randomization, rescue medication start date/time (see Section 7.3), time to rescue medication start date/time in hours (see Section 6.3.4.3), pain level at on-study migraine attack onset, MBS at on-study migraine attack onset, and reason for exclusion from the mITT population sample (see Section 6.2.1). Missing data and complete cases (see Section 6.3.5.2) will be flagged at each time point for each endpoint. See Section 6.3.5.2 for efficacy outcomes.

6.3.3.1 Pain Freedom at 2 Hours Post-Dose

Pain freedom is defined as having a pain level of none at a single time point post-dose.

For the co-primary endpoint, subjects who meet both of the following criteria will be classified as responders:

- Pain level of none at 2 hours post-dose, i.e., in the 2-hour post-dose analysis window
- No intervening rescue medication taken at or before 2 hours post-dose, i.e., rescue medication start date/time missing or > {eDiary finding date/time in the 2-hour post-dose analysis window}.

Subjects who are not classified as responders and have any of the following will be classified as failures:

- Intercurrent event: Rescue medication taken at or before 2 hours post-dose (RM=F), i.e., (rescue medication start date/time – study drug start date/time) ≤ 135 minutes, the upper bound of the 2-hour post-dose analysis window (see Section 7.5)
- Mild, moderate, or severe pain at 2 hours post-dose, i.e., in the 2-hour post-dose analysis window
- Missing pain level at 2 hours post-dose (NC=F), i.e., in the 2-hour post-dose analysis window.

Principal Analyses

Pain freedom outcomes at 2 hours post-dose will be summarized by treatment group (see Section 6.3.5.2). Outcomes will be summarized analogously for each subgroup level of all efficacy subgroups of interest specified in Section 6.1.3.

The percentages of subjects with pain freedom at 2 hours post-dose will be compared pairwise between each BHV-3500 treatment group and placebo using Cochran-Mantel-Haenszel (CMH) tests stratified by prophylactic migraine medication use at randomization (yes, no). In these analyses, the NC=F and RM=F methods will be applied. The following statistics will be presented:

- Response rate (i.e., "n/N" and percentage), ASE, and 98.3% CI by randomization stratum for each treatment group
- Overall response rate (i.e., "n/N" and percentage), ASE, and 98.3% CI for each treatment group
- Percentage difference between treatment groups (BHV-3500 – placebo), ASE, 98.3% CI, and p-value by randomization stratum
- Stratified percentage difference between treatment groups (BHV-3500 – placebo), ASE, 98.3% CI, and p-value.

The stratified percentage difference between each BHV-3500 treatment group and placebo will be tested at a Bonferroni-corrected alpha level of 0.0167. A BHV-3500 treatment group will be considered to be superior to placebo for this co-primary endpoint if the p-value for the stratified percentage difference is < 0.0167.

The principal analysis will be repeated unstratified for each subgroup level of all efficacy subgroups of interest specified in Section 6.1.3.

Sensitivity Analyses

Sensitivity analyses will include the following:

- Complete cases: The principal analysis will be repeated using NC=M, i.e., subjects who have missing pain level in the 2-hour post-dose analysis window are excluded. First, the RM=F method of handling intervening rescue medication use will be applied. Next, subjects with missing data in the 2-hour analysis window will be excluded. The same statistics as the principal analysis will be presented.
- Multiple imputation: The principal analysis will be repeated using the copy from reference multiple imputation approach with m=20 imputations to impute missing pain data at 2 hours post-dose. The fully conditional specification (FCS) method is used with a generalized logit distribution. Covariates may include prophylactic migraine medication use at randomization (yes or no), sex, pain level at on-study migraine attack onset (moderate or severe), historical number of moderate to severe migraine attacks per month ($<$ median, $\geq$ median), and MBS at on-study migraine attack onset (nausea, phonophobia, or photophobia). First, the RM=F

method of handling intervening rescue medication use will be applied. Next, missing data in the 2-hour post-dose analysis window will be imputed for subjects who are not missing any of the covariates (subjects missing any of the covariates will be considered failures). The same statistics as the principal analysis will be presented.

- Varying response rate imputation: The principal analysis will be repeated by imputing missing pain data at 2 hours post-dose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, the RM=F method of handling intervening rescue medication use will be applied. Next, missing data in the 2-hour post-dose analysis window will be imputed. The following statistics will be presented: stratified percentage difference between treatment groups (BHV-3500 – placebo), ASE, 98.3% CI, and p-value.

6.3.3.2 MBS Freedom at 2 Hours Post-Dose

MBS freedom is defined as the MBS reported at on-study migraine attack onset and being absent at a single time point post-dose, e.g., subjects who report nausea as the MBS at onset before taking study drug and have nausea absent at 2 hours post-dose.

For the co-primary endpoint, subjects who meet both of the following criteria will be classified as responders:

- MBS reported at migraine attack onset before taking study drug and being absent at 2 hours post-dose, i.e., in the 2-hour post-dose analysis window
- No intervening rescue medication taken at or before 2 hours-dose, i.e., rescue medication start date/time missing or > {eDiary finding date/time in the 2-hour post-dose analysis window}.

Subjects who are not classified as responders and have any of the following will be classified as failures:

- MBS missing at on-study migraine attack onset (see Section 7.6.3.2)
- Intercurrent event: Rescue medication taken at or before 2 hours post-dose (RM=F) i.e., (rescue medication start date/time – study drug start date/time) ≤ 135 minutes, the upper bound of the 2-hour post-dose analysis window (see Section 7.5)
- MBS present at 2 hours post-dose, e.g., nausea reported as MBS at onset and nausea present in the 2-hour post-dose analysis window
- MBS missing at 2 hours post-dose (NC=F), e.g., nausea reported as MBS at onset and nausea status missing in the 2-hour post-dose analysis window.

Principal Analyses

MBS freedom outcomes at 2 hours post-dose will be summarized by treatment group (see Section 6.3.5.2). Outcomes will be summarized analogously for each subgroup level of all efficacy subgroups of interest specified in Section 6.1.3 plus MBS at on-study migraine attack onset (nausea, phonophobia, photophobia).

The percentages of subjects with MBS freedom at 2 hours post-dose will be compared pairwise between each BHV-3500 treatment group and placebo using CMH tests stratified by prophylactic migraine medication use at randomization (yes, no). In these analyses, the NC=F and RM=F methods will be applied. The same statistics will be presented as those for the principal analysis of pain freedom at 2 hours post-dose (see Section 6.3.3.1). The stratified percentage difference between each BHV-3500 treatment group and placebo will be tested at a Bonferroni-corrected alpha level of 0.0167. A BHV-3500 treatment group will be considered to be superior to placebo for this co-primary endpoint if the p-value for the stratified percentage difference is < 0.0167.

The principal analysis will be repeated unstratified for each subgroup level of all efficacy subgroups of interest specified in Section 6.1.3 plus MBS at on-study migraine attack onset (nausea, phonophobia, photophobia).

Sensitivity Analyses

Sensitivity analyses will include the following:

- Complete cases: The principal analysis will be repeated using NC=M, i.e., subjects who have missing MBS status in the 2-hour post-dose analysis window are excluded. First, subjects whose MBS at on-study migraine attack onset is missing will be classified as failures. Next, the RM=F method of handling intervening rescue medication use will be applied. Finally, subjects with missing data in the 2-hour post-dose analysis window will be excluded.
- Multiple imputation: The principal analysis will be repeated using the copy from reference multiple imputation approach with m=20 imputations to impute missing MBS status in the 2-hour post-dose analysis window. First, subjects whose MBS at on-study migraine attack onset is missing will be classified as failures. Next, the RM=F method of handling intervening rescue medication use will be applied. Finally, missing data in the 2-hour post-dose analysis window will be imputed.
- Varying response rate imputation: The principal analysis will be repeated by imputing missing MBS at 2 hours post-dose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, subjects whose MBS at on-study migraine attack onset is missing will be classified as failures. Next, the RM=F method of handling intervening rescue medication use will be applied. Finally, missing data in the 2-hour post-dose analysis window will be imputed.

See Section 6.3.3.1 for additional details about methods and the presentation of statistics.

6.3.4 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be evaluated for mITT subjects, unless specified otherwise.

If the co-primary endpoint tests are both significant for a BHV-3500 treatment group versus placebo, then the secondary endpoints are tested for that BHV-3500 treatment group versus placebo using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at alpha=0.0167. The endpoints are tested in the order shown in Section 1.2.2.

A by-subject listing of outcomes for pain relief, nausea freedom, phonophobia freedom, photophobia freedom, and return to normal function will be provided for randomized subjects at each time point post-dose. The listing will also include prophylactic migraine medication use at randomization and time to rescue medication start date/time in minutes (see Section 6.3.4.3), as well as nausea status, phonophobia status, photophobia status, and functional disability level at on-study migraine attack onset. Missing data and complete cases will be flagged at each time point for each endpoint. See Section 6.3.5.2 for efficacy outcomes over time.

6.3.4.1 Pain Relief at 30 Minutes, 60 Minutes and at 2 Hours Post-Dose

Pain relief is defined as a pain level of none or mild at a single time point post-dose.

Pain relief outcomes at 2 hours post-dose will be summarized by treatment group (see Section 6.5.3.2).

At each time point post-dose (30 minutes, 60 minutes, and 2 hours), treatment group comparisons of the percentage of subjects with pain relief will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.3.1).

6.3.4.2 Return to Normal Function at 30 Minutes, 60 Minutes, and 2 Hours Post-Dose

Return to normal function is defined as a functional disability level of normal at a single time point post-dose for subjects with functional disability (mildly impaired, severely impaired, requires bedrest) at on-study migraine attack onset. Thus, all analyses of return to normal function will be based on mITT subjects with functional disability at on-study migraine attack onset.

Return to normal function outcomes at 2 hours post-dose will be summarized by treatment group (see Section 6.3.5.2).

At each time point post-dose (30 minutes, 60 minutes, and 2 hours), treatment group comparisons of the percentage of subjects with return to normal function will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.3.1).

6.3.4.3 Probability of Rescue Medication Use within 24 Hours Post-Dose

Analyses will be based on evaluable mITT subjects, i.e., mITT subjects with rescue medication start date on or before study drug start date + 1 day and missing rescue medication start time will be excluded. Time to rescue medication use will be measured from the study drug start date/time to the rescue medication start date/time.

No analysis window around the 24-hour post-dose time point will be used.

Rescue Medication Use Within 24 Hours Post-Dose

Rescue medication use within 24 hours post-dose is defined as time to rescue medication use ≤ 24 hours.

Treatment group comparisons of the percentage of subjects using rescue medication within 24 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom, except that the NC=F and RM=F methods will not be applied because they are not applicable to this endpoint (see Section 6.3.3.1).

Time to Rescue Medication Use Through 24 Hours Post-Dose

Time to rescue medication use through 24 hours post-dose will be assessed by treatment group as follows:

- Kaplan-Meier (KM) plot and table using 2-hour time intervals (i.e., 0 to 2, > 2 to 4, ... , > 24). The KM plot will display the percentage of subjects taking rescue medication within 24 hours post-dose on the y-axis versus time in hours on the x-axis.
- Time-to-event distribution table (hours), including a log-rank p-value (BHV-3500 versus placebo).

See Section 7.1.1.1 for time-to-event plot and table attributes. Rescue medication use through 24-hours post-dose will be considered as an event in these time-to-event analyses. Subjects who do not take rescue medication within 24 hours post-dose will be censored at 24 hours and 1 minute (i.e., 1441 minutes).

6.3.4.4 Freedom from Photophobia, Phonophobia or Nausea at 2 Hours Post-Dose

Freedom from each symptom (nausea, phonophobia, photophobia) at 2 hours post-dose will be assessed separately.

Symptom freedom is defined as a symptom absent at a single time point post-dose for subjects with the symptom present at on-study migraine attack onset. Thus, all analyses of symptom freedom will be based on mITT subjects with the symptom present at on-study migraine attack onset (see Section 7.6.3.2), e.g., nausea freedom at a post-dose time point will be based on subjects with nausea present at onset.

Symptom freedom outcomes at 2 hours post-dose will be summarized by treatment group (see Section 6.3.5.2).

Treatment group comparisons of the percentage of subjects with symptom freedom at 2 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.3.1).

6.3.4.5 Sustained Pain Relief from 2 to 24 Hours Post-Dose

Sustained pain relief from 2 to 24 hours post-dose is defined as pain level of none or mild at all time points from 2 to 24 hours post-dose.

Subjects who meet all of the following criteria will be classified as responders:

- Pain level of none or mild at all time points from 2 to 24 hours post-dose, i.e., in the 2 to 24-hour post-dose analysis windows
- Missing data at ≤ 1 time point from 3 to 8 hours post-dose, i.e., in the 3, 4, 6, or 8-hour post-dose analysis windows
- No intervening rescue medication taken at or before 24 hours post-dose, i.e., rescue medication start date/time missing or > {eDiary finding date/time in the 24-hour post-dose analysis window}.

Otherwise, subjects who are not responders and have any of the following will be classified as failures:

- Intercurrent event: Rescue medication taken at or before 24 hours post-dose (RM=F), i.e., (rescue medication start date/time – study drug start date/time) ≤ 25 hours, the upper bound of the 24-hour post dose analysis window
- Moderate or severe pain at any time point from 2 to 24 hours post-dose, i.e., in the 2, 3, 4, 6, 8 or 24-hour post-dose analysis window
- Missing pain level at 2 or 24 hours post-dose (NC=F), i.e., in the 2 or 24-hour post-dose analysis window
- Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F), i.e., in the 3, 4, 6, or 8-hour post-dose analysis window.

Sustained pain relief from 2 to 24 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Responder: mild or no pain at all time points from 2 to 24 hours post-dose, missing data at ≤ 1 time point from 3 to 8 hours post-dose, and no intervening rescue medication taken at or before 24 hours post-dose

- Failure
  - Rescue medication taken at or before 24 hours post-dose (RM=F)
  - Moderate or severe pain at any time point from 2 to 24 hours post-dose
    - Severe pain
    - Moderate pain
  - Missing pain level at 2 or 24 hours post-dose (NC=F)
  - Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F).

Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain relief from 2 to 24 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.3.1).

6.3.4.6 Sustained Pain Relief from 2 to 48 Hours

Sustained pain relief from 2 to 48 hours post-dose is defined as pain level of none or mild at all time points from 2 to 48 hours post-dose.

Subjects who meet all of the following criteria will be classified as responders:

- Pain level of none or mild at all time points from 2 to 48 hours post-dose, i.e., in the 2 to 48-hour post-dose analysis windows
- Missing data at ≤ 1 time point from 3 to 8 hours post-dose, i.e., in the 3, 4, 6, or 8-hour post-dose analysis windows
- No intervening rescue medication taken at or before 48 hours post-dose, i.e., rescue medication start date/time missing or > {eDiary finding date/time in the 48-hour post-dose analysis window}.

Otherwise, subjects who are not classified as responders and have any of the following will be classified as failures:

- Intercurrent event: Rescue medication taken at or before 48 hours post-dose (RM=F), i.e., (rescue medication start date/time – study drug start date/time) ≤ 49 hours, the upper bound of the 48-hour post dose analysis window
- Moderate or severe pain at any time point from 2 to 48 hours post-dose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour post-dose analysis window
- Missing pain level at 2, 24, or 48 hours post-dose (NC=F), i.e., in the 2, 24, or 48-hour post-dose analysis window

- Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F), i.e., in the 3, 4, 6, or 8-hour post-dose analysis window.

Sustained pain relief from 2 to 48 hours outcomes will be summarized for mITT subjects by treatment group as the number and percentage of subjects in the following categories:

- Responder: mild or no pain at all time points from 2 to 48 hours post-dose, missing data at ≤ 1 time point from 3 to 8 hours post-dose, and no intervening rescue medication taken at or before 48 hours post-dose
- Failure
    - Rescue medication taken at or before 48 hours post-dose (RM=F)
    - Moderate or severe pain at any time point from 2 to 48 hours post-dose
        - Severe pain
        - Moderate pain
    - Missing pain level at 2, 24, or 48 hours post-dose (NC=F)
    - Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F).

Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain relief from 2 to 48 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.3.1).

6.3.4.7 Sustained Pain Freedom from 2 to 24 Hours

Sustained pain freedom from 2 to 24 hours post-dose is defined as pain level of none at all time points from 2 to 24 hours post-dose.

Subjects who meet all of the following criteria will be classified as responders:

- Pain level of none at all time points from 2 to 24 hours post-dose, i.e., in the 2 to 24-hour post-dose analysis windows
- Missing data at ≤ 1 time point from 3 to 8 hours post-dose, i.e., in the 3, 4, 6, or 8-hour post-dose analysis windows
- No intervening rescue medication taken at or before 24 hours post-dose (see Section 6.3.4.5).

Subjects who are not classified as responders and have any of the following will be classified as failures:

- Intercurrent event: Rescue medication taken at or before 24 hours post-dose (RM=F; see Section 6.3.4.5)

- Mild, moderate or severe pain at any time point from 2 to 24 hours post-dose, i.e., in the 2, 3, 4, 6, 8 or 24-hour post-dose analysis window
- Missing pain level at 2 or 24 hours post-dose (NC=F), i.e., in the 2 or 24-hour post-dose analysis window
- Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F), i.e., in the 3, 4, 6, or 8-hour post-dose analysis window.

Sustained pain freedom from 2 to 24 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Responder: no pain at all time points from 2 to 24 hours post-dose, missing data at ≤ 1 time point from 3 to 8 hours post-dose, and no intervening rescue medication taken at or before 24 hours post-dose
- Failure
    - Rescue medication taken at or before 24 hours post-dose (RM=F)
    - Mild, moderate or severe pain at any time point from 2 to 24 hours post-dose
        - Severe pain
        - Moderate pain
        - Mild pain
    - Missing pain level at 2 or 24 hours post-dose (NC=F)
    - Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F).

Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain freedom from 2 to 24 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.3.1).

6.3.4.8 Sustained Pain Freedom from 2 to 48 Hours

Sustained pain freedom from 2 to 48 hours post-dose is defined as pain level of none at all time points from 2 to 48 hours post-dose.

Subjects who meet all of the following criteria will be classified as responders:

- Pain level of none at all time points from 2 to 48 hours post-dose, i.e., in the 2 to 48-hour post-dose analysis windows
- Missing data at ≤ 1 time point from 3 to 8 hours post-dose, i.e., in the 3, 4, 6, or 8-hour post-dose analysis windows
- No intervening rescue medication taken at or before 48 hours post-dose (see Section 6.3.4.6).

Subjects who are not classified as responders and have any of the following will be classified as failures:

- Intercurrent event: Rescue medication taken at or before 48 hours post-dose (RM=F; see Section 6.3.4.6)
- Mild, moderate or severe pain at any time point from 2 to 48 hours post-dose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour post-dose analysis window
- Missing pain level at 2, 24, or 48 hours post-dose (NC=F), i.e., in the 2, 24, or 48-hour post-dose analysis window
- Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F), i.e., in the 3, 4, 6, or 8-hour post-dose analysis window.

Sustained pain freedom from 2 to 48 hours outcomes will be summarized for mITT subjects by treatment group as the number and percentage of subjects in the following categories:

- Responder: no pain at all time points from 2 to 48 hours post-dose, missing data at ≤ 1 time point from 3 to 8 hours post-dose, and no intervening rescue medication taken at or before 48 hours post-dose
- Failure
    - Rescue medication taken at or before 48 hours post-dose (RM=F)
    - Mild, moderate or severe pain at any time point from 2 to 48 hours post-dose
        - Severe pain
        - Moderate pain
        - Mild pain
    - Missing pain level at 2, 24, or 48 hours post-dose (NC=F)
    - Missing pain level at > 1 time point from 3 to 8 hours post-dose (NC1=F).

Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain freedom from 2 to 48 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.3.1).

6.3.4.9 Pain Relapse from 2 to 48 Hours Post-Dose

Pain relapse from 2 to 48 hours post-dose is defined as pain of mild, moderate, or severe at any time point post-dose after 2 hours post-dose for subjects with pain level of none at 2 hours post-dose. Thus, analyses of pain relapse will be based on mITT subjects with pain freedom at 2 hours post-dose (see Section 6.3.3.1).

Subjects who meet all of the following criteria will be classified as non-relapsers:

- Pain level of none at all time points after 2 hours post-dose, i.e., in the 3 to 48-hour post-dose analysis windows
- Missing data at ≤ 1 time point after 2 hours post-dose, i.e., in the 3, 4, 6, 8, 24, or 48-hour post-dose analysis window
- No intervening rescue medication taken at or before 48 hours post-dose (see Section 6.3.4.6).

Otherwise, subjects who are not classified as non-relapsers and have any of the following will be classified as relapsers:

- Intercurrent event: Rescue medication taken at or before 48 hours post-dose (RM=F; see Section 6.3.4.6)
- Mild, moderate or severe pain at any time point after 2 hours post-dose, i.e., in the 3, 4, 6, 8, 24, or 48-hour post-dose analysis window
- Missing pain level at > 1 time point after 2 hours post-dose (NC1=F), i.e., in the 3, 4, 6, 8, 24, or 48-hour post-dose analysis window.

Pain relapse from 2 to 48 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Non-relapser: no pain at all time points after 2 hours post-dose, missing data at ≤ 1 time point after 2 hours post-dose, and no intervening rescue medication taken at or before 48 hours post-dose
- Relapser
    - Rescue medication taken at or before 48 hours post-dose (RM=F)
    - Mild, moderate or severe pain at any time point after 2 hours post-dose
        - Severe pain
        - Moderate pain
        - Mild pain
    - Missing pain level at > 1 time point after 2 hours post-dose (NC1=F).

Relapser subcategories are mutually exclusive, because subjects who meet more than 1 relapse criterion will be classified according to the first relapse criterion met; in case of ties, the first relapse subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with pain relapse from 2 to 48 hours post-dose will use analogous methods as the principal analysis of the co-primary endpoint of pain freedom with NC1=F and RM=F (see Section 6.3.3.1).

6.3.4.10 Overall Summary of Primary and Secondary Endpoints

An overall summary of treatment comparisons of all primary and secondary endpoints tested hierarchically will present the following statistics:

- Overall response rate (i.e., "n/N" and percentage) and 98.3% CI for each treatment group
- Stratified percentage difference between treatment groups (BHV-3500 – placebo), 98.3% CI, and p-value.

Analyses will be based on principal methods described in Sections 6.3.3 and 6.3.4. Endpoints will be displayed in the order presented in Sections 1.2.1 and 1.2.2. P-values that are determined to be significant based on the testing hierarchy will be flagged.

A forest plot of treatment comparisons of all primary and secondary endpoints tested hierarchically will be produced for each treatment group comparison of BHV-3500 versus placebo based on the overall summary. Each plot will display the following statistics:

- Overall response rate (i.e., "n/N" and percentage) for the BHV-3500 treatment group and placebo
- Stratified percentage difference between treatment groups (BHV-3500 – placebo) and 98.3% CI.

Percentage differences with p-values that are determined to be significant based on the testing hierarchy will be flagged. Note that each plot will display results for *no* intervening rescue medication use within 24 hours post-dose and *no* pain relapse from 2 to 48 hours post-dose so that positive percentage differences will favor BHV-3500 for these secondary endpoints.

6.3.5 Exploratory Efficacy Endpoints

All exploratory efficacy endpoints will be evaluated for mITT subjects, unless specified otherwise.

Any p-values presented for exploratory efficacy endpoints are for descriptive purposes only, and not included in the hierarchical testing.

6.3.5.1 Return to Normal Function at 24 Hours

Return to normal function outcomes at 24 hours post-dose will be summarized by treatment group (see Section 6.3.5.2).

6.3.5.2 Efficacy at Each Post-Dose Time Point

Efficacy Outcomes Over Time: Principal Analyses

Efficacy outcomes will be summarized for mITT subjects by treatment group as the number and percentage of subjects in categories (responder; failure; failure subcategories) at each time point from 15 minutes through 48 hours post-dose. Subjects who are not classified as responders at a time point will be classified as failures. Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the specified hierarchy for an endpoint will be chosen. Percentages for response rates will also be shown with exact Clopper-Pearson 98.3% CIs.

Outcomes will be presented separately for each of the following efficacy endpoints: pain freedom, MBS freedom, pain relief, nausea freedom, phonophobia freedom, photophobia freedom, and return to normal function. These analyses will use the NC=F and RM=F methods to align with principal analyses of co-primary and secondary endpoints (see Sections 6.3.3.1 and 6.3.3.2). Outcomes category nomenclature is as follows:

- "at time point" means in the analysis window corresponding to that post-dose time point
- "No intervening rescue medication taken at or before time point" means rescue medication start date/time missing or > {eDiary finding date/time in the analysis window corresponding to that post-dose time point}
- "Rescue medication taken at or before time point" means (rescue medication start date/time – study drug start date/time) ≤ upper bound of the analysis window corresponding to that post-dose time point (see Section 7.5).

Outcomes for mITT subjects will be presented over time as described below. Subjects who are not included in the mITT population sample will have the following outcomes in by-subject listings:

- Randomized subjects not in the mITT population sample: "Not mITT"
- mITT subjects with absent or missing symptom status at on-study migraine attack onset for nausea freedom, photophobia freedom, and photophobia freedom: "Not evaluable: symptom absent at onset" or "Not evaluable: symptom missing at onset"
- mITT subjects with normal or missing functional disability level at on-study migraine attack onset for return to normal function: "Not evaluable: normal function at onset" or "Not evaluable: missing disability level at onset".

Pain Freedom Outcomes Over Time

Outcomes categories are defined as:

- Responder: No pain at time point and no intervening rescue medication taken at or before time point

- Failure
  - Rescue medication taken at or before time point (RM=F)
  - Mild, moderate or severe pain at time point
    - Severe pain
    - Moderate pain
    - Mild pain
  - Missing pain level at time point (NC=F).

MBS Freedom Outcomes Over Time

Outcome categories are:

- Responder: MBS reported at on-study migraine attack onset before taking study drug, MBS absent at time point, and no intervening rescue medication taken at or before time point
- Failure
  - Missing MBS at on-study migraine attack onset
  - Rescue medication taken at or before time point (RM=F)
  - Nausea reported as MBS at on-study migraine attack onset and present at time point
  - Phonophobia reported as MBS at on-study migraine attack onset and present at time point
  - Photophobia reported as MBS at on-study migraine attack onset and present at time point
  - Missing MBS status at time point (NC=F).

Pain Relief Outcomes Over Time

Outcome categories are defined as:

- Responder: Mild or no pain at time point and no intervening rescue medication taken at or before time point
- Failure
  - Rescue medication taken at or before time point (RM=F)
  - Moderate or severe pain at time point
    - Severe pain
    - Moderate pain
  - Missing pain level at time point (NC=F).

Nausea Freedom, Photophobia Freedom and Phonophobia Freedom Outcomes Over Time

Freedom from each symptom (nausea, phonophobia, and photophobia) will be evaluated separately. Analyses will be based on mITT subjects with the symptom present at on-study migraine attack onset (see Section 7.6.3.2).

Outcomes categories are defined as:

- Responder: symptom absent at time point and no intervening rescue medication taken at or before time point
- Failure
  - Rescue medication taken at or before time point (RM=F)
  - Symptom present at time point
  - Missing symptom status at time point (NC=F).

Return to Normal Function Outcomes Over Time

Analyses will be based on mITT subjects with functional disability at on-study migraine attack onset.

Outcomes categories are defined as:

- Responder: normal at time point and no intervening rescue medication taken at or before time point
- Failure
  - Rescue medication taken at or before time point (RM=F)
  - Functional disability at time point
    - Requires bedrest
    - Moderately impaired
    - Mildly impaired
  - Missing functional disability level at time point (NC=F).

Complete Cases Over Time: Sensitivity Analyses

Response rates corresponding to efficacy outcomes over time will also be presented using complete cases for each of the following efficacy endpoints: pain freedom, MBS freedom, pain relief, nausea freedom, phonophobia freedom, photophobia freedom, and return to normal function. Percentages for response rates will also be shown with exact Clopper-Pearson 98.3% CIs.

In these sensitivity analyses, subjects who are missing data in a post-dose time point analysis window will be excluded at that time point (NC=M). Results for the co-primary endpoints of

pain freedom and MBS freedom at 2 hours post-dose will be the same as those for the complete cases sensitivity analyses (see Sections 6.3.3.1 and 6.3.3.2).

For MBS freedom, the following conventions will be applied: (1) first, subjects whose MBS at on-study migraine attack onset is missing will be classified as failures; (2) next, the RM=F method of handling intervening rescue medication use will be applied; (3) finally, subjects with missing data in the analysis window will be excluded.

For all other endpoints, the RM=F method of handling intervening rescue medication use will be applied first, and then subjects with missing data in the analysis window will be excluded.

Time-to-Event Efficacy Endpoints

The following time-to-event endpoints will be analyzed:

- Pain freedom through 4 hours post-dose
- Pain freedom through 8 hours post-dose
- MBS freedom through 8 hours post-dose for subjects with MBS reported at on-study migraine attack onset
- Pain relief through 4 hours post-dose
- Pain relief through 8 hours post-dose
- Nausea freedom through 8 hours post-dose for subjects with nausea present at on-study migraine attack onset
- Phonophobia freedom through 8 hours post-dose for subjects with phonophobia present at on-study migraine attack onset
- Photophobia freedom through 8 hours post-dose for subjects with photophobia present at on-study migraine attack onset
- Return to normal function through 8 hours post-dose for subjects with functional disability at on-study migraine attack onset.

Analyses are based on non-missing, post-dose efficacy data relevant to each endpoint.

For a given time-to-event endpoint, subjects are considered to have an event through *X* hours (*X* = 4 or 8) if the first post-dose eDiary finding date/time defining response is (1) at or before the upper bound of the *X*-hour analysis window in minutes (see Table 5), and (2) is before the imputed rescue medication start date/time, if not missing (see Section 7.3).

Otherwise, subjects who do not have an event through *X* hours will be censored at the earliest of the following: (1) upper bound of the *X*-hour analysis window + 1 minute; (2) time from the study drug start date/time to the imputed rescue medication start date/time, if the time is at or before the upper bound of the *X*-hour analysis window in minutes; (3) time from the study drug start date/time to the last non-missing finding date/time defining the endpoint, if the time was before the lower bound of *X*-hour analysis window in minutes.

For each endpoint listed above, time to event will be assessed by treatment group as follows:

- KM plot and table using the following time intervals post-dose: 0 to 15, >15 to 30, > 30 to 45, > 45 to 60, > 60 to 90, > 90 to 120, > 120 to 180, > 180 to 240, > 240 to 360, > 360 to 495, and > 495 minutes. The KM plot will display the percentage of subjects with the event on the y-axis versus time in minutes on the x-axis. See Section 7.1.1.1 for KM plot and table attributes.
- Time-to-event distribution table (minutes), including a log-rank p-value (BHV-3500 versus placebo).

See Section 7.1.1.1 for time-to-event plot and table attributes.

6.4 Pharmacokinetics

No pharmacokinetic data will be collected in this study.

6.5 Safety

Safety analyses will be conducted on treated subjects by as-treated treatment group (i.e., the actual treatment received) and All BHV-3500.

Safety measures will include: AEs, laboratory tests, vital signs, physical measurements, electrocardiograms (ECGs), S-STS, and nasal inspection.

Analysis periods are pre-treatment and on-treatment (see Section 7.4).

Values and changes from baseline in safety findings (e.g., laboratory tests, vital signs and physical measurements, ECGs) and S-STS endpoints will be summarized as continuous variables descriptively at baseline and the end of treatment visit. These analyses will be based on observed data without imputation and regardless of rescue medication use. For the change from baseline, subjects must have non-missing paired measurements at baseline and end of treatment visit to be evaluable. If a subject has multiple values in the end of treatment analysis window (see Section 7.5), then the last non-missing value in the analysis period will be used; in the case of a tie, the value collected from the central laboratory, if applicable, will be used.

6.5.1 Adverse E vents

AEs will be displayed in tables and listings by SOC and PT, unless specified otherwise. AEs by SOC and PT will be displayed in descending order of overall frequency within SOC and PT.

See Section 7.6.1 for AE start date imputation, AE counting rules in frequency tables, treatment-emergent adverse events (TEAEs), and AEs of special interest.

The following by-subject listings of all AEs will be provided for enrolled subjects: AEs; deaths; SAEs; and AEs leading to study drug discontinuation. TEAEs will be flagged.

6.5.1.1 AE Overview

An AE overview without SOC and PT will present the number and percentage of subjects with any of the following AEs: any AE; mild AE; moderate AE; severe AE; AE related to study drug; SAE; SAE related to study drug; AE leading to study drug discontinuation; and AE leading to death.

An AE overview will be produced for each analysis period (pre-treatment, on-treatment) for treated subjects.

An AE will be considered related to study drug if the relationship is not reported (missing), unlikely related, possibly related, or related.

6.5.1.2 Pre-Treatment AEs by SOC and PT

Pre-treatment AEs will be summarized by SOC and PT for treated subjects for the following endpoints:

- AEs by severity (total, mild, moderate, severe, moderate or severe, not reported)
- SAEs.

6.5.1.3 On-Treatment AEs by SOC and PT

On-treatment AEs will be summarized by SOC and PT for treated subjects for the following endpoints:

- AEs by severity
- TEAEs by severity
- AEs related to study drug by severity
- SAEs
- AEs leading to study drug discontinuation
- Hepatic-related AEs *
- Cardiovascular AEs *
- Suicidality AEs *.

AEs of special interest are asterisked ("*").

6.5.2 Laboratory Tests

Laboratory tests will be analyzed using results from the central laboratory and local laboratory tests reported on CRFs.

Tables, listings and figures (TLFs) will present results in both SI (Systeme Internationale) and United States (US) unit systems, if applicable.

LDL cholesterol and triglycerides will be analyzed as separate laboratory test parameters according to fasting status: fasting (i.e., fasting status of yes); not fasting (i.e., fasting status not equal to yes, including no, unknown, not reported, missing, etc.); overall.

Clinically significant laboratory abnormalities will be identified as grade 3 to 4 laboratory test results according to numeric laboratory test criteria in Common Technical Criteria for Adverse Events (CTCAE) Version 5.0 (2017) if available; otherwise according to Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017).

Laboratory tests of clinical interest for analyses will include the following:

- Hematology: hemoglobin#, hematocrit, red blood cell count, white blood cell count# with differential (including basophils, basophils/leukocytes, eosinophils, eosinophils/leukocytes, lymphocytes*#, lymphocytes/leukocytes, monocytes, monocytes/leukocytes, neutrophils#, neutrophils/leukocytes), and platelets#
- Serum chemistry: alanine aminotransferase (ALT)#, AST#, albumin#, alkaline phosphatase (ALP)#, bicarbonate#, total bilirubin (TBL)#, calcium#*, chloride*, cholesterol (total)#, creatine kinase#, creatinine#, CPK (with fractionation, if available), direct bilirubin, estimated glomerular filtration rate (eGFR)# using the modification of diet in renal disease (MDRD) formula, glucose@*, HDL cholesterol, hemoglobin A1C, indirect bilirubin, LDL cholesterol@, lactate dehydrogenase#, lipase, phosphorus, potassium#*, protein, sodium#*, triglycerides#, urea nitrogen, uric acid (urate)@
- Urinalysis: pH, specific gravity, ketones, nitrites, urobilinogen, urine hemoglobin, leukocyte esterase, urine protein@, and urine glucose@.

Tests marked with "*" are bidirectional, tests marked with "#" will be graded according to CTCAE, and tests marked with "@" will be graded according to DAIDS.

By-subject listings of the following select laboratory test groups will be provided for enrolled subjects: hematology; serum chemistry; urinalysis (US units only); pregnancy (US units only); endocrinology, serology, drug screen, and miscellaneous laboratory tests (US units only). In addition, a by-subject listing of LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) will also be provided for enrolled subjects for both US and SI units, which will display all LFT results over time for those with select LFT elevations (ALT or AST > 3 x ULN; ALP or TBL > 2 x ULN) at any time point. Listings will display toxicity grades, if applicable.

6.5.2.1 Laboratory Test Abnormalities

On-treatment laboratory test abnormalities will be summarized as the number and percentage of treated subjects in the following frequency tables:

- Worst (highest) on-treatment laboratory test abnormality for each graded laboratory test. Toxicity grade categories will be Grade 0, Grade 1 to 2, Grade 3 to 4, Grade 3, and Grade 4. Bidirectional tests will be assessed separately for each component (e.g., calcium, low; calcium, high).

- Laboratory test toxicity grade shift from baseline to the worst on-treatment toxicity grade for each graded laboratory test. Toxicity grade categories will be Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4. Bidirectional tests will be assessed separately for each component (e.g., calcium, low; calcium, high).
- Laboratory test low/normal/high shifts from baseline to any abnormal on-treatment value for each laboratory test with normal ranges. Categories will be low, normal, and high. Note that categories do not depend on US or SI units. Subjects with both low and high values in the on-treatment analysis period will be counted in both low and high categories for that period and given laboratory test (thus, these categories are not mutually exclusive). Subjects must have only normal values in the on-treatment analysis period to be counted in the normal category for that period and given laboratory test.

Tables will present results by laboratory tests alphabetically within laboratory test group, as applicable.

6.5.2.2 Liver Function Test Elevations

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

The number and percentage of subjects with LFT elevations will be summarized separately for each analysis period (pre-treatment, on-treatment) for treated subjects.

The frequency table of LFT elevations will include the following endpoints:

- Cumulative elevations:
  - ALT > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - AST > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - ALT or AST > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - TBL > 1 x, > 1.5 x, and > 2 x ULN
  - ALP > 1 x, > 1.5 x, and > 2 x ULN
- Mutually exclusive elevations:
  - ALT > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - AST > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - ALT or AST > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - TBL > ULN to ≤ 1.5 x ULN, > 1.5 x ULN to ≤ 2 x ULN, and > 2 x ULN
  - ALP > ULN to ≤ 1.5 x ULN, > 1.5 x ULN to ≤ 2 x ULN, and > 2 x ULN

- Composite elevations:
  - ALT or AST > 3 x ULN and TBL > 1.5 x ULN
  - ALT or AST > 3 x ULN and TBL > 2 x ULN
  - ALT or ALT > 3 x ULN concurrent with TBL > 2 x ULN with exact Clopper-Pearson 95% CIs. Concurrent is defined as elevations on the same laboratory test collection date.
  - ALT or ALT > 3 x ULN concurrent with TBL > 2 x ULN and ALP ≤ 2 x ULN with exact Clopper-Pearson 95% CIs. Concurrent is defined as elevations on the same laboratory test collection date.
  - ALT or AST > 3 x ULN concurrent with AEs of interest: nausea, vomiting, anorexia, abdominal pain, and fatigue. For a given analysis period, an LFT elevation is concurrent with an AE of interest if the imputed AE start date is +/- 7 days inclusive of the LFT collection date; both the LFT collection date and the imputed AE start date must also be in the analysis period. The following PTs will be used to identify the AEs of interest: nausea, vomiting, anorexia, fatigue, and those containing "abdominal pain."

Subjects must have non-missing on-study LFT data (i.e., ALT, AST, TBL, or ALP) to be included.

LFT ULN Shifts from Baseline to Worst Elevation

LFT ULN shifts from baseline to the worst (highest) on-treatment elevation will be summarized as the number and percentage of treated subjects in the following categories: ≤ ULN, > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN (US and SI units are identical, U/L). LFTs will be limited to ALT and AST.

eDISH Scatter Plot

An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot will display the maximum TBL ratio of value to ULN on the y-axis versus the maximum ALT ratio of value to ULN on the x-axis by treatment group (excluding All BHV-3500), where both maxima will be on treatment but not necessarily concurrent. Both axes will be on the $\log_{10}$ scale. Ratios < 0.1 x ULN will be set to 0.1. Sample sizes in the legend will represent subjects with paired ratios. A horizontal reference line will be placed at 2 x ULN, and a vertical reference line will be placed at 3 x ULN. 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", and the upper right quadrant will be labeled "Possible Hy's Law Range."

6.5.2.3 Laboratory Test Change From Baseline

Values and changes from baseline in laboratory tests will be summarized as continuous variables at baseline and the end of treatment visit.

6.5.3 Vital Signs and Physical Measurements

Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate. In tables, only vital signs measured in the sitting position will be included.

Physical measurements will include weight and BMI.

A by-subject listing of vital signs and physical measurements will be provided for enrolled subjects.

6.5.3.1 Vital Sign and Physical Measurement Change From Baseline

Values and changes from baseline in vital sign and physical measurement parameters will be summarized as continuous variables at baseline and the end of treatment visit.

6.5.3.2 Vital Sign and Physical Measurement Abnormalities

On-treatment vital sign and physical measurement abnormalities will be summarized as the number and percentage of subjects in the following categories:

- Systolic blood pressure (mmHg): < 90 , > 140, > 160
- Diastolic blood pressure (mmHg): < 50, > 90, > 100
- Heart rate (bpm): < 60, > 100
- Temperature (C): < 36, > 38
- Respiratory rate (breaths/min): < 12, > 20
- Weight change from baseline: ≤ -7%, ≥ 7%.

6.5.4 Electrocardiogram

ECG parameters will include RR, QRS, PR, QT, QTcF, and ventricular heart rate.

A by-subject listing of ECG results will be provided for enrolled subjects.

6.5.4.1 ECG Change from Baseline

Values and changes from baseline in ECG parameters will be summarized as continuous variables at baseline and the end of treatment visit.

6.5.4.2 ECG Interpretation Shift from Baseline to Worst Category

The ECG interpretation shift from baseline to the worst on-treatment category will be summarized as the number and percentage of subjects with normal, abnormal, and clinically significant abnormal interpretations.

6.5.4.3 ECG Abnormalities

On-treatment ECG abnormalities will be summarized as the number and percentage of subjects in the following categories:

- QTcB (msec): > 450, > 480, > 500
- QTcB interval increase from baseline (msec): > 30, > 60
- QTcF (msec): > 450, > 480, > 500
- QTcF interval increase from baseline (msec): > 30, > 60

6.5.5 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.

Values and changes from baseline in the self-reported S-STS ideation subscale, behavior subscale, and total score will be summarized as continuous variables at baseline and the end of treatment visit. The number and percentage of subjects in each change from baseline category (i.e., < -1, -1, no change, 1, > 1) will also be presented for the ideation subscale, behavior subscale, and total score.

The by-subject S-STS listing will include study visit and assessment date. If the total score > 0, then responses to all questions will be presented; otherwise, only the ideation subscale, behavioral subscale, and total scores will be presented.

6.5.6 Nasal Inspection

Nasal inspections will evaluate evidence of edema and inflammation in the left and right nostrils with yes or no responses. Abnormalities are considered to be “yes” responses.

A by-subject listing of nasal inspection will be provided for enrolled subjects.

6.5.6.1 Nasal Inspection Abnormalities

On-treatment nasal inspection abnormalities will be summarized for each parameter as the number and percentage of subjects with abnormalities for the following parameters: nasal edema or nasal inflammation in either nostril; nasal edema in left nostril; nasal edema in right nostril; nasal inflammation in left nostril; nasal inflammation in right nostril. Percentages will be based on subjects with non-missing data for each parameter.

6.5.6.2 Nasal Inspection Evidence Shift from Baseline

Nasal inspection evidence shifts from baseline to an on-treatment abnormality will be summarized for each parameter (nasal edema in left nostril; nasal edema in right nostril; nasal inflammation in left nostril; nasal inflammation in right nostril) as the number and percentage of subjects in each evidence category (yes or no).

6.5.7 Safety Narratives

A by-subject listing of safety narrative subject identifiers will be provided for the following select events as columns: all deaths for enrolled subjects; all SAEs for enrolled subjects; all AEs leading to discontinuation of study therapy for treated subjects; on-treatment events of special interest for treated subjects: hepatic-related AEs; cardiovascular AEs; suicidality AEs; AST or ALT > 3 x ULN. The listing will flag subjects with events, as well as display total numbers of subjects with each event and any event in the first row.

6.5.8 Outcomes Research

Outcomes research endpoints are exploratory and will be assessed at 24 hours post-dose using the eDiary.

Analyses will be based on observed data without imputation and regardless of rescue medication use.

6.5.8.1 PoM

The PoM is a 5-point rating scale that measures the patient's preference of study medication to previous medications to treat migraine pain. The 5 preference categories are: much better, I prefer this medication; slightly better than the previous medication; about the same as the previous medication; slightly worse than the previous medication; and much worse, I prefer my previous medication.

Combined categories will include the following: (1) prefer study medication, defined as much better or slightly better; (2) prefer previous medication, defined as slightly worse or much worse.

PoM will be summarized as the number and percentage of treated subjects in each preference category (including combined categories) by as-treated treatment group and All BHV-3500.

Percentages for categories will be based on subjects with non-missing data, along with exact Clopper-Pearson 95% CIs for each percentage.

PoM will also be summarized analogously by as-randomized treatment group for mITT subjects: (1) overall; (2) by pain freedom outcome at 2 hours post-dose (responder, failure) for subjects who are included in the complete cases sensitivity analysis of pain freedom at 2 hours post-dose (see Section 6.3.3.1).

A by-subject listing of PoM will be provided for enrolled subjects.

6.5.8.2 MQoL

Impact of treatment on patient-reported quality of life is assessed using the MQoL Version 3.0, which is a 15-item questionnaire that has been validated in migraine patients to measure the short-term impact of treatment within 24 hours. The MQoL consists of 15 items across the following 5 domains: (1) work functioning; (2) social functioning; (3) energy/vitality; (4) migraine symptoms; (5) feelings/concerns.

Subjects will rate the negative effect of migraine headache and accompanying symptoms on each item on a 7-point scale, where 1 indicates maximum impairment of quality of life and 7 indicates no impairment.

There are 3 items within each domain. Each domain has a maximum score of 21 and a minimum score of 3. Items in domains are as follows:

- Work functioning: (1) ability to do normal everyday work, (2) ability to operate machinery or a motor vehicle, and (3) ability to stay alert.
- Social functioning: (1) interactions with people who are close to you *, (2) interactions with other people *, and (3) ability to enjoy life.
- Energy/vitality: (1) energy level, (2) ability to have a good night's sleep, and (3) mood.
- Migraine symptoms: (1) have throbbing head pain, (2) have increased sensitivity to light and/or noise, and (3) have nausea.
- Feelings/concerns: (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.

Responses to items asterisked (“*”) are: a very great deal; a great deal; a good deal; a moderate amount; some; very little; and none. Responses to all other items are: all of the time; most of the time; a good bit of the time; some of the time; a little of the time; hardly any of the time; or none of the time.

The total score will be calculated as the sum of item scores to all 15 questions. All 15 item scores must be non-missing; otherwise, the total score will be considered missing.

Each domain score will be calculated as the sum of the 3 item scores pertaining to that domain. All 3 item scores must be non-missing; otherwise, the domain score will be considered missing.

MQoL total, domain, and item scores will be summarized by as-treated treatment group and All BHV-3500 for treated subjects as (1) continuous variables, and (2) the number and percentage of subjects in the following categories:

- Total score: 15 to 30, 31 to 45, 46 to 60, 61 to 75, 76 to 90, and 91 to 105
- Domain score: 3 to 6, 7 to 10, 11 to 14, 15 to 18, and 19 to 21
- Item score: 7-point scale categories defined previously
- Overall change since dose of medication: very much better; moderately better; a little better; no change; a little worse moderately worse; very much worse. Combined categories will include: (1) very much or moderately better; (2) not very much or moderately better, defined as the last 5 categories combined.

Percentages for categories will be based on subjects with non-missing data.

MQoL total, domain, and item scores will be summarized analogously by as-randomized treatment group for mITT subjects.

A by-subject listing of MQoL will be provided for enrolled subjects, and will present the total score, domain scores, and item scores for each domain.

7 CONVENTIONS

7.1 General

7.1.1 Output Layout

All programmed outputs (i.e., TLFs) will be formatted and numbered according to the latest version of Biohaven Standard Outputs for CSRs.

A list of TLFs and corresponding templates will be presented separately in a mock TLF document corresponding to this SAP.

7.1.1.1 Time-to-Event Tables and Plots

Time-to-event endpoints will be summarized with KM tables displaying the following at each time interval:

- Number of subjects at risk, defined as those who did not have the event just prior to the start of the interval and who were not censored prior to the interval
- Number of subjects with events, defined as those who had the event for the first time during the interval
- Number of subjects censored, defined as those who did not have the event and whose censoring date/time is in the interval
- Cumulative probability of having the event with lower and upper CI limits, based on the KM product limit method.

Time-to-event endpoints will also be summarized with corresponding KM plots displaying 100 times the cumulative probability of having the event on the y-axis and time on the x-axis, including the number of subjects at risk at each time point below the x-axis.

Time-to-event distributions of endpoints will be summarized with the following descriptive statistics: number and percentage of subjects with events; number and percentage of subjects censored in or before the last time interval; number and percentage of subjects censored in the last time interval; median time to event with CI using the method of Brookmeyer and Crowley.

CI levels will be 98.3% for efficacy endpoints and 95% for all other endpoints.

7.1.1.2 By-Subject Listings

Unless specified otherwise, by-subject listings will be sorted by randomization status (randomized, not randomized), site-subject ID, and additional variables such as time points, as applicable. Listings will display site-subject ID and as-randomized treatment group.

By-subject listings will display site-subject ID and "(Age/Sex/Race)" stacked together in the same column using the following conventions:

- Age at informed consent will be displayed truncated to an integer.
- Sex will be displayed abbreviated as "F" for female and "M" for male.
- Race will be displayed abbreviated as "A" for Asian", "B" for Black or African American, "I" for American Indian or Alaska Native, "M" for multiple, "N" for Native Hawaiian or Other Pacific Islander, and "W" for White.

A footnote will describe race abbreviations as applicable, e.g., "Race: A = Asian, B = Black or African American, I = American Indian or Alaska Native, M = Multiple, N = Native Hawaiian or Other Pacific Islander, W = White". See Section 6.2.4.1 for multiple race. Missing age, sex, or race will be displayed as a single blank space.

Note that "(Age/Sex/Race)" will not be displayed in listings of randomization scheme and codes, batch numbers, and demographics.

Listings of non-study medications, eDiary migraine characteristics, safety parameters, and outcomes research parameters will show both study day and treatment day (see Section 7.5). Other listings will display study day only, if applicable.

7.1.2 Descriptive Statistics

For categorical variables, summary tabulations of the number and percentage of subjects within each category will be presented. If applicable, a "not reported" category for missing data will also be presented. Percentages will be displayed as: "<0.1" if 0 < percentage < 0.1; ">99.9" if 99.9 < percentage < 100; 0 count without a percentage; and rounded to 1 decimal place otherwise. Measures of variance (standard error [SE], CI) will be presented to 1 decimal place.

For continuous variables, descriptive statistics (e.g., n, mean, median, standard deviation (SD), minimum, and maximum) will be presented. The minimum and maximum 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. Measures of variance (SD, SE, CI) will be presented with the precision of the data + 2 decimal places. For percent change from baseline, the minimum and maximum will be presented in 0 decimal places; mean and percentiles will be presented in 1 decimal place; and measures of variance in 2 decimal places. P-values < 0.0001 will be presented as "<0.0001". Otherwise, p-values will be presented in 4 decimal places.

7.1.3 Counting Rules

Frequency tables of the following endpoints will present the number and percentage of unique subjects with an event: significant protocol deviations; medical history; non-study medications; AEs; laboratory test shifts from baseline; vital sign and physical measurement abnormalities; ECG interpretation shifts from baseline and abnormalities; nasal inspection abnormalities. Thus, for these endpoints, multiple occurrences of the same event will be counted only once per subject.

Percentages in frequency tables will be calculated against the number of subjects in the group (i.e., sample sizes in column headers), unless specified otherwise. For safety findings and OR endpoints, percentages will be calculated on a subset of subjects as follows:

- In analyses of the worst abnormality or category in an analysis period, subjects must have a non-missing measurement in the analysis period to be included for a given parameter.
- In shift from baseline analyses of an analysis period, subjects must have a non-missing measurement at baseline and in the analysis period to be included for a given parameter.

7.2 Subgroups

Triptan non-responders are identified using the Prior Triptan Response CRF, which captures reasons for discontinuing triptans taken historically. 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 4 efficacy-related questions are as follows:

- 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.

Responses to each question are "most or all of the time", "some of the time", and "rarely". A subject is considered to have failed a drug for efficacy reasons if they responded "most or all of the time" to any of the 4 questions.

A triptan non-responder is defined as any subject that fails 2 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.

7.3 Derived Dates

Derived dates are defined as follows:

- Study drug start date/time: Earliest study medication date and time from the eDiary Migraine Report or Study Medication Intake Report (see Section 7.6.3.1). This date is used to define analysis periods.
  - eDiary Migraine Report
    - If the subject answered "yes" to taking study medication mistakenly already, then the following conventions will be applied depending when drug was reported taken:
      - Today: study drug start date will be set to the finding date, and the study drug start time will be set to the time of study medication taken, if available.
      - Yesterday: study drug start date will be set to the finding date – 1 day, and study drug start time will be set to the time of study medication taken, if available.
      - Other: study drug start date will be set to the date of study medication taken, if available.
    - Otherwise, if the subject answered "no" to taking study medication mistakenly already and answered "yes" to confirming having taken study medication, then the study drug start date/time will be set to the finding date/time.
  - Study Medication Intake Report: Study medication date/time.
- Rescue medication start date/time: Earliest rescue medication date/time (see Section 6.2.5.2). Missing time is considered to be earlier than non-missing time on the same date.
- Imputed rescue medication start date/time: This will be used only for time-to-event efficacy analyses in Section 6.3.5.2, and not for time to rescue medication use analyses in Section 6.3.4.3.
  - If the rescue medication start date and time are both not missing, then the imputed rescue medication start date/time will be set to the rescue medication start date/time.
  - If the rescue medication start time is missing and the rescue medication start date is equal to the study drug start date, then the imputed rescue medication start date/time will be set to the study drug start date/time.
  - Otherwise, if the rescue medication start time is missing and the rescue medication start date is equal to a post-dose eDiary finding date with non-missing efficacy data, then the imputed rescue medication start date/time will be set to the first eDiary finding date/time corresponding to non-missing efficacy data.
  - Otherwise, if the rescue medication start time is missing and rescue medication start date is equal to the study drug start date + 1 day, then the imputed rescue medication start

date/time will be set to the study drug start date/time + upper bound of the *X*-hour analysis window (see Table 5).

- Last contact date: (1) Complete death date, if it exists; (2) otherwise, the maximum complete date of the following: AE start/stop; ECG; eDiary finding; eDiary study drug start; informed consent; IWRS randomization; laboratory collection; non-study medication start/stop; physical measurement; procedure; rating scale; questionnaire; study completion/discontinuation from Study Exit Status CRF; vital sign; visit.

No date imputations are performed on these derived dates. Complete dates are those with valid, non-missing day, month, and year.

7.4 Analysis Periods

Analysis periods are defined as follows:

- Pre-treatment: measurement date/time at or before the study drug start date/time. This period is used to derive baseline values and to assess pre-treatment endpoints.
- On-treatment: measurement date/time after the study drug start date/time. Note that AEs with imputed start date equal to the study drug start date are part of this period.
- On-study: measurement date/time after the randomization date/time.

See Section 7.3 for derived dates for determining analysis periods.

If measurement time is missing or not collected for a parameter, then the measurement date will be compared to the derived date.

7.5 Analysis Visit Windows

Study days are calculated from the IWRS randomization date as follows:

- Measurement date – randomization date + 1, if measurement date ≥ randomization date
- Measurement date – randomization date, if measurement date < randomization date.

Treatment days are calculated from the study drug start date as follows:

- Measurement date – study drug start date + 1, if measurement date ≥ study drug start date
- Measurement date – study drug start date, if measurement date < study drug start date.

Analysis windows for safety and outcomes research parameters are presented in Table 4.

For longitudinal analyses of safety and outcomes research parameters, the end of treatment analysis visit window is defined as measurement date/time > study drug start date/time.

Table 4: Analysis Windows for Safety and Outcomes Research Parameters

Evaluation	Analysis-Specified Interval
Screening	≤ Study Day -1
Randomization	Study Day 1
Post-Randomization	≥ Study Day 2

See Section 7.6.3.2 for efficacy analysis windows.

7.6 Domain-Specific Derivations

7.6.1 Adverse Events

7.6.1.1 Imputed AE Start Dates

Imputed AE start dates will be used to classify AEs in analysis periods, and to determine LFT elevations concurrent with AEs of interest.

Complete dates are those with non-missing day, month, and year that are valid and consistent with the standard international calendar.

- Examples of complete dates: 01JAN2013, 31DEC2013;
- Example of non-complete dates: missing, 31FEB2013, MAY2013, 2013, “unknown”, “ongoing”, “continuing”, “NA”.

Partially complete dates are those with either (1) missing day with complete month and year, or (2) missing day and month with complete year. Examples: MAY2013, 2013.

To derive the imputed AE start date and numeric imputed start date flag, the following algorithm is used if the investigator term is non-missing:

1. If the reported start date is complete, then the imputed start date is set to the reported start date and the numeric imputed start date flag is set to 0 (No).
2. If the reported start date is partially complete then the following algorithm is used:
    a. Calculate a surrogate date as the first complete date from the following list (in order of precedence):
        i. First active study medication date of any study medication;
        ii. Informed consent date;
        iii. Visit date corresponding to the visit at which the event was reported.

        If a complete date is not available for any of these 3 dates, then the surrogate date is set to missing.
    b. Calculate the derived date as the earliest possible date:
        i. If only year is provided, then set the derived date to January 1st of that year. e.g., 2004 => 01JAN2004

ii. If year and month are provided, then set the derived date to the first day of the month.
e.g., AUG2004 => 01AUG2004

3. Compare the derived date with the surrogate date as follows:
   a. If (1) the derived date is on or after the surrogate date or (2) the surrogate date is missing, then set the imputed start date to the derived date.
   e.g., surrogate date = 05JAN2004, partial date = SEP2004, derived date = 01SEP2004 => imputed start date = 01SEP2004
   b. If the derived date is before the surrogate date and the surrogate date is consistent with the partial date provided for the start date, then set the imputed start date to the surrogate date.
   e.g., surrogate date = 05JAN2004, partial date = JAN2004, derived date = 01JAN2004 => imputed start date = 05JAN2004
   c. If the derived date is before the surrogate date and the surrogate date is not consistent with the partial date provided for the start date, then set the imputed start date to be the latest possible date based on the partial start date information provided.
      i. If only year is provided, then set the imputed start date to December 31st of that year.
      e.g., surrogate date = 05JAN2004, partial date = 2003, derived date = 01JAN2003, imputed start date = 31DEC2003
      ii. If year and month and provided, then set the imputed start date to the last day of the month.
      e.g., surrogate date = 05JAN2004, partial date = DEC2003, derived date = 01DEC2003, imputed start date = 31DEC2003

The numeric imputed start date flag is set to 1 (Yes).

4. If the reported start date is not complete and not partially complete, then the imputed start date is set to the first complete date from the following list (in order of precedence):
   a. First active study medication date of any study medication;
   b. Informed consent date;
   c. Visit date corresponding to the visit at which the event was reported.

If a complete date is not available for any of these 3 dates, then the imputed start date is set to missing and the numeric imputed start date flag is set to 0 (No). Otherwise, the numeric imputed start date flag is set to 1 (Yes).

7.6.1.2 AE Frequency Table

An AE will be considered to have developed during an analysis period if the imputed AE start date is in the analysis period. See Section 7.6.1.1 for AE start date imputation.

Frequency tables will present the number and percentage of subjects experiencing AEs during analysis periods. The following counting rules will apply:

- In AE tables by severity, SOC, and PT, a subject's worst severity of a PT during the analysis period will be reported. A subject will contribute only once to the count for a given AE SOC or PT, regardless of the number of events.
    - Severities may include total (i.e., any severity including missing), mild, moderate, and severe.
    - Example: If subject has 1 mild rash AE and 2 moderate rash AEs, then the subject will be counted under rash once in both the total and moderate severities.
- In AE tables by SOC and PT, a subject will contribute only once to the count for a given AE SOC or PT, regardless of the number of events.
- In AE tables by PT, a subject will contribute only once to the count for a given AE PT, regardless of the number of events.

7.6.1.3 Treatment-Emergent AEs

Treatment-emergent AEs (TEAEs) are those that developed, worsened, or became serious during the on-treatment analysis period relative to the pre-treatment analysis period. For a given subject and PT, the following will apply:

- An AE developed on treatment if the first occurrence (as determined by the imputed start date) is on treatment.
- An AE worsened on treatment if the worst on-treatment severity is greater than the worst pre-treatment severity (including not reported).
- An AE became serious on treatment if (1) at least one on-treatment AE has serious status of "yes", and (2) no pre-treatment AE has serious status of "yes".

Thus, TEAEs are a subset of on-treatment AEs.

7.6.1.4 AEs of Special Interest

Hepatic-Related AEs

Hepatic-related AE PTs will include the following:

- "Hepatic disorders" SMQ: All PTs except those in "Congenital, familial, neonatal and genetic disorders of the liver" SMQ.

Cardiovascular AEs

Cardiovascular AE PTs will include the following:

- "Conditions associated with central nervous system haemorrhages and cerebrovascular accidents" SMQ: Narrow PTs

- "Ischaemic central nervous system vascular conditions" SMQ: Narrow PTs
- "Embolic and thrombotic events, arterial" SMQ: peripheral arterial occlusive disease; peripheral arterial reocclusion; peripheral artery angioplasty; peripheral artery bypass; peripheral artery occlusion; peripheral artery stent insertion; peripheral artery thrombosis
- "Ischaemic colitis" SMQ: Narrow PTs
- "Ischaemic heart disease" SMQ
  - "Myocardial infarction" SMQ: Narrow PTs
  - "Other ischaemic heart disease" SMQ: Narrow PTs

Suicidality AEs

Suicidality AE PTs will include the following: completed suicide; suicide attempt; suicidal ideation.

7.6.2 Non-Study Medications

Non-study medication imputed start and stop dates will be derived in order to categorize non-study medications as prior or concurrent.

See Section 7.6.1.1 for the definitions of complete dates and partially complete dates.

7.6.2.1 Imputed Non-Study Medication Start Dates

To derive the imputed medication start date and numeric imputed start date flag, the following algorithm is used if the reported medication is non-missing:

1. If reported start date is complete:
   - Imputed start date is set to reported start date.
   - Numeric imputed start date flag is set to 0 (No).

2. If reported start date is partially complete:
   - Imputed start date is set to the earliest possible date based on the partial start date information provided.
     e.g., SEP2018 => 01SEP2018, 2018 => 01JAN2018
   - Numeric imputed start date flag is set to 1 (Yes).

3. If reported start date is not complete and not partially complete then do
   if informed consent date is complete then do
   if reported end date is at or before informed consent date then do
   if birth date is complete then do
   imputed start date is set to birth date

```
        numeric imputed start date flag is set to 1 (Yes)
      end
      else do (i.e., birth date is not complete)
       imputed start date is set to missing
       numeric imputed start date flag is set to 0 (No)
      end
    else if reported end date is after informed consent date then do
      imputed start date is set to informed consent date
      numeric imputed start date flag is set to 1 (Yes)
    end
   end
   else do (i.e., informed consent date is not complete)
    if birth date is complete then do
     imputed start date is set to birth date
     numeric imputed start date flag is set to 1 (Yes)
    end
   else do
    imputed start date is set to missing
    numeric imputed start date flag is set to 0 (No)
   end
  end
 end
```

7.6.2.2 Imputed Non-Study Medication Stop Dates

To derive the imputed medication stop date and numeric stop date imputed flag, the following algorithm is used if the reported term is non-missing:

1. If reported stop date is complete:
   - Imputed stop date is set to the reported stop date.
   - Numeric stop date imputed flag is set to 0 (No).
2. If reported stop date is partially complete:
   - Imputed stop date is set to the earlier of (a) death date or (b) last possible stop date based on the partial reported stop date information provided.
     e.g., if death date missing, then SEP2013 => 30SEP2013, 2013 => 31DEC2013
   - Numeric stop date imputed flag is set to 1 (Yes).
3. If reported stop date is not complete and not partially complete:
   - Imputed stop date is set to the earlier of (a) death date or (b) most recent raw database creation date.
   - Numeric stop date imputed flag is set to 1 (Yes).

7.6.2.3 Non-Study Medication Types

Non-study medication types will include prior, previous, current, and concomitant.

Prior medications are defined as those taken before study drug, i.e., imputed start or stop date < study drug start date. These include the following subtypes:

- Previous medications, defined as those taken before informed consent, i.e., those with an imputed start or stop date < informed consent date
- Current medications, defined as those taken on or after informed consent and before study drug, i.e., those with (1) informed consent date ≤ imputed start or stop date < study drug start date or (2) imputed start date ≤ informed consent date < study drug start date - 1 ≤ imputed stop date.

Concomitant medications are defined as those taken on or after study drug, i.e., study drug start date ≤ imputed start or stop date.

Listings will display abbreviated medication types. Note that a medication may be classified into multiple types.

7.6.3 eDiary Data

7.6.3.1 Study Medication

eDiary Migraine Report

If the subject answered "yes" to taking study medication mistakenly already before using the eDiary, then the eDiary Migraine Report will collect study medication time if the subject reported taking it today or yesterday; otherwise, only the study medication date will be collected.

Otherwise, if the subject answered "no" to taking study medication mistakenly already, had a current pain level of moderate or severe, and answered "yes" to confirming having taken study medication, then the eDiary Migraine Report will record the time the subject has confirmed taking study medication (i.e., finding date/time) as the study medication time.

eDiary Study Medication Intake Report

Subjects who took study medication without using the eDiary will have the study medication date and time reported by the site on the eDiary Study Medication Intake Report.

7.6.3.2 Migraine Characteristics

The following migraine characteristics will be collected at migraine attack onset in the eDiary Migraine Report and post-dose from 15 minutes through 48 hours (e.g., 15, 30, 45, 60, and 90 minutes; 2, 3, 4, 6, 8, 24 and 48 hours) in the eDiary Post-Dose Migraine Report:

- Pain level (none, mild, moderate, severe)
- MBS (nausea, phonophobia, photophobia) in the Migraine Report only
- Nausea status (present, absent)
- Nausea level (none, mild, moderate, severe)
- Phonophobia status (present, absent)
- Phonophobia level (none, mild, moderate, severe)
- Photophobia status (present, absent)
- Photophobia level (none, mild, moderate, severe)
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura (yes, no) in the Migraine Report only.

The eDiary will allow subjects to report one result per time point per migraine characteristics parameter.

In general, if subjects answered "no" to taking study medication mistakenly already, had current pain level of moderate or severe, and did not use other headache medications, then the eDiary Migraine Report will collect all parameters listed above.

Otherwise, if subjects answered "yes" to taking study medication mistakenly already, then the eDiary Migraine Report will not collect the following parameters: most bothersome symptom, current pain level, nausea status, phonophobia status, and photophobia status. Instead, if the subject provided the time of study medication taken, then the eDiary Migraine Report will collect nausea level, phonophobia level, photophobia level, pain level and functional disability level at the time study drug was taken. Thus, for these subjects at on-study migraine attack onset, a symptom status (nausea, phonophobia, photophobia) of absent is defined as a level of none, and present is defined as a level of mild, moderate, or severe.

Windows for post-dose efficacy measurements (15, 30, 45, 60, 90 minutes; 2, 3, 4, 6, 8, 24, and 48 hours) will be automatically assigned by the eDiary as shown in Table 5.

Table 5: eDiary Automated Efficacy Analysis Windows

Post-Dose Evaluation	Analysis-Specified Interval	Target Time
15 minutes	10 to 20 minutes	Study medication start time + 15 minutes
30 minutes	25 to 35 minutes	Study medication start time + 30 minutes
45 minutes	40 to 50 minutes	Study medication start time + 45 minutes
60 minutes	55 to 65 minutes	Study medication start time + 60 minutes
90 minutes	85 to 95 minutes	Study medication start time + 90 minutes
2 hours	1 hour 45 minutes to 2 hours 15	Study medication start time + 2 hours
3 hours	2 hours 45 minutes to 3 hours 15	Study medication start time + 3 hours
4 hours	3 hours 45 minutes to 4 hours 15	Study medication start time + 4 hours
6 hours	5 hours 45 minutes to 6 hours 15	Study medication start time + 6 hours
8 hours	7 hours 45 minutes to 8 hours 15	Study medication start time + 8 hours
24 hours	23 to 25 hours	Study medication start time + 24 hours
48 hours	47 to 49 hours	Study medication start time + 48 hours