BioShin Limited

BHV3000-310: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine

BHV3000-310

Statistical Analysis Plan

Version: 1.0

Date：28Jan2022

Sponsor Approval Page

BHV3000-310: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine

BHV3000-310

Statistical Analysis Plan

Version: 1.0

Project Statistician: PPD

Company Name: PPD

Signature: PPD PPD

Review Statistician: PPD

Company Name: PPD

Signature: PPD Date: PPD

Approved by Sponsor: PPD

Company Name: BioShin Limited

Signature: _____ Date PPD

Approved by Sponsor Statistician: PPD

Company Name: BioShin Limited

Signature: _____ Date: PPD

Modification History

Version	Version Date	Author	Description
1.0	2022/1/28	PPD	FINAL VERSION

Table of Contents

Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DAIDS	Division of AIDS
ECG	Electrocardiogram
EOT	End of Treatment
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eGFR	Estimated Glomerular Filtration Rate
FDS	Functional Disability Scale
IP=F	Taking IP prior to reporting the MBS, or failure to report an MBS =Failure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NC=F	Non-Completers=Failure
NC1=F	Non-Completer with more than 1 missing data point = Failure
NRS	Numeric Rating Scale
NSAID	Non- Steroidal Anti-inflammatory
ODT	Orally Disintegrating Tablet
PPS	Per Protocol Set
PT	Preferred Term
QTc	QT Interval Corrected for Heart Rate
RM=F	Rescue Medication=Failure
SAE	Serious Adverse Event

Abbreviation	Description
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
ULN	Upper Limit of Normal
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1 Introduction

This document presents the statistical analysis plan (SAP) for BioShin Limited, Protocol BHV3000-310: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) 75 mg for the Acute Treatment of Migraine.

This SAP is based on the BHV3000-310, V2.3, protocol dated 25-May-2021. 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.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of rimegepant 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 two hours post dose.

2.2 Secondary Objectives

2.2.1 Key Secondary Objectives

1. To compare rimegepant to placebo on pain relief at 2 hours post-dose
2. To compare rimegepant to placebo on the ability to function normally at 2 hours post-dose as reported on the Functional Disability scale (FDS)
3. To compare rimegepant to placebo on the Use of Rescue Medications through 24 hours post-dose
4. To compare rimegepant to placebo on sustained pain freedom from 2 to 24 hours post-dose
5. To compare rimegepant to placebo on sustained pain freedom from 2 to 48 hours post-dose

2.2.2 Other Secondary Objectives

1. To compare rimegepant to placebo on pain freedom at 15, 30, 45, 60 and 90 minutes post-dose
2. To compare rimegepant to placebo on freedom from MBS at 15, 30, 45, 60 and 90 minutes post-dose
3. To compare rimegepant to placebo for the incidence of pain relapse from 2 to 48 hours post-dose

2.3 Exploratory Objectives

1. To compare rimegepant to placebo on pain relief at all post-dose timepoints.
2. To compare rimegepant to placebo on pain freedom at all post-dose timepoints.
3. To compare rimegepant to placebo on freedom from MBS at all post-dose timepoints.
4. To compare rimegepant to placebo on freedom from functional disability at all post-dose timepoints.
5. To compare rimegepant to placebo on freedom from phonophobia at all post-dose time points
6. To compare rimegepant to placebo on freedom from photophobia at all post-dose time points
7. To compare rimegepant to placebo on freedom from nausea at all post-dose time points
8. To compare rimegepant to placebo on sustained pain relief from 2 to 24 hours post-dose
9. To compare rimegepant to placebo on sustained pain relief from 2 to 48 hours post-dose
10. To compare rimegepant to placebo on freedom from MBS from 2 to 24 hours post-dose
11. To compare rimegepant to placebo on freedom from MBS from 2 to 48 hours post-dose
12. To compare rimegepant to placebo on the ability to function normally from 2 to 24 hours post-dose as reported on the FDS
13. To compare rimegepant to placebo on the ability to function normally from 2 to 48 hours post-dose as reported on the FDS

3 Study Design

This is a double-blind, randomized, regional, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the acute treatment of moderate or severe migraine. The study drug will be rimegepant presented in a 75 mg Orally Disintegrating Tablet (ODT) or matching placebo.

The study will randomize approximately 1,430 subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no) and country (Korea or China).

A subject whose usual migraine attack results in headache pain of moderate or severe intensity and who is otherwise found acceptable for entry into this trial based on inclusion and exclusion

criteria will first participate in the screening phase (3 – 28 day period). Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.

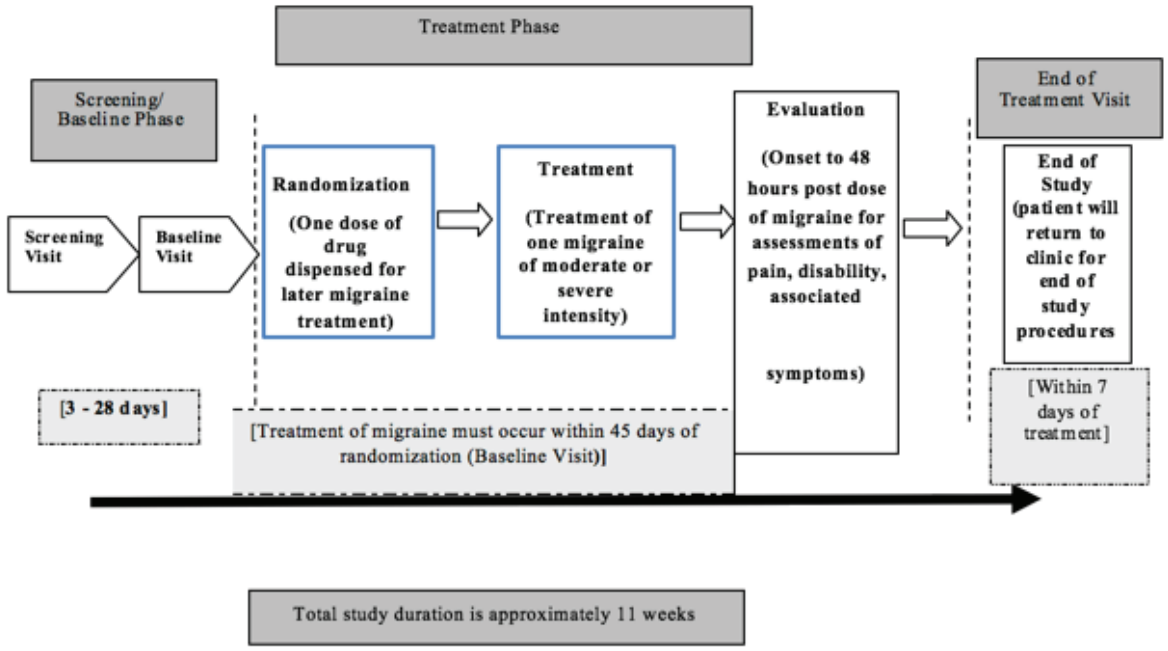
After randomization, the subject will be dispensed a single dose of the double-blind study medication that will be taken at the time a migraine attack reaches moderate or severe pain intensity (described below) on the numeric rating scale (NRS) as indicated in the electronic diary (eDiary). The subject will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe pain intensity and only after they have identified their most bothersome migraine-associated symptom (phonophobia, photophobia or nausea) in the eDiary. The subject will complete an eDiary for forty-eight hours after taking study medication. The subject will telephone the study center immediately if a severe or serious adverse event occurs.

Subjects will record efficacy data in their eDiary. This includes the following: onset time of headache, intensity of the headache prior to and at time of taking study medication. Subject should not dose with study medication until headache reaches moderate to severe intensity. Headache severity will be recorded using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (four-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Subjects who experience reduction of headache pain to a mild intensity or pain free intensity level will be considered to have achieved pain relief. The subject who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (and after the two hour assessments have been completed on the eDiary) will be permitted to use the following rescue medications: aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine), naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. If at the end of 48-hours after dosing with study medication (but before the End of Treatment Visit) subjects are in need of migraine relief, they may take their prescribed standard of care medications, including triptans if not contraindicated, provided all of the assessments have been completed on the eDiary. Exclusionary rescue medication such as opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed on this study. Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the subject will be permitted to take the same rescue therapy as outlined above. In all circumstances, the subject will always continue to complete his or her eDiary for up to forty-eight hours after consuming the study medication. During the 45 days the subject is participating in the study, if the subject has a nonqualifying migraine (mild migraine) or a migraine that they do not treat with study medication, the subject is permitted to use only the following medications: aspirin, ibuprofen, naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen.

Subjects will return to the study site within 7 days (+2) of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety

(including vital signs, laboratory tests, and electrocardiography). 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. All subjects must return unused study medication and eDiary to the study center.

Study Schematic



4 Endpoints

4.1 Primary Endpoints

The co-primary endpoints are the following:

Pain freedom at 2 hours will be assessed using the number of evaluable subjects that report no pain at two hours post-dose. Pain will be measured on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

Freedom from the MBS at 2 hours will be assessed using the number of evaluable subjects that report the absence of their MBS at 2 hours post-dose. The MBS (nausea, phonophobia or photophobia) will be measured using a binary scale (0=absent, 1=present).

4.2 Secondary Endpoints

4.2.1 Key Secondary Endpoints

1. Pain Relief at 2 hours post-dose, will be assessed using the number of subjects that report a pain level of moderate or severe at baseline and then report a pain level of none or mild at two hours post-dose.

2. The proportion of subjects able to function normally, at 2 hours post-dose, will be assessed using the number of subjects that self-report as "normal" on the FDS in the subset of subjects that report any level of disability just prior to taking study medication.

3. The use of rescue medication will be assessed using the number of subjects that take rescue medication within 24 hours after administration of study medication (rimegepant or placebo).

4. Sustained pain freedom, from 2 to 24 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.

5. Sustained pain freedom, from 2 to 48 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.

4.2.2 Other Secondary Endpoints

1. Pain freedom at 15, 30, 45, 60 and 90 minutes will be assessed using the number of subjects that report a pain level of moderate or severe just before taking study medication and then report a pain level of none at the timepoint of interest.

2. Freedom from the MBS at 15, 30, 45, 60 and 90 minutes will be assessed using the number of subjects that report the absence of their MBS at the time point of interest.

3. Pain relapse will be assessed using the number of subjects that are pain free at 2 hours post-dose and then have a migraine of any pain severity (response of: 2 or 3 on the 4-point scale) within 48 hours after administration of study medication.

4.3 Safety Endpoints

The safety endpoints are the following:

- Adverse events and serious adverse events;
- Laboratory tests (hematology, blood chemistry/electrolyte, lipid panel, estimated glomerular filtration rate (eGFR), urinalysis, urine drug screen);
- 12-lead ECG;
- Physical examination;
- Vital signs.

4.4 Exploratory Endpoints

1. Pain Relief at 15, 30, 45, 60, and 90 minutes, 3, 4, 6, 8, 24, and 48 hours post-dose will be assessed using the number of subjects that report a pain level of moderate or severe at baseline and then report a pain level of none or mild at the timepoint of interest.

2. Pain freedom at 3, 4, 6, 8, 24, and 48 hours post-dose will be assessed using the number of evaluable subjects that report no pain at the timepoint of interest.

3. Freedom from MBS at 3, 4, 6, 8, 24, and 48 hours post-dose will be assessed using the number of evaluable subjects that report the absence of their MBS at the timepoint of interest.

4. The proportion of subjects able to function normally, at all post-dose timepoints except 2 hours, will be assessed using the number of subjects that self-report as "normal" on the FDS in the subset of subjects that report any level of disability just prior to taking study medication.

5. Freedom from phonophobia at all post-dose time points will be assessed using the number of evaluable subjects that report the absence of their phonophobia at the timepoint of interest.

6. Freedom from photophobia at all post-dose time points will be assessed using the number of evaluable subjects that report the absence of their photophobia at the timepoint of interest.

7. Freedom from nausea at all post-dose time points will be assessed using the number of evaluable subjects that report the absence of their nausea at the timepoint of interest.

8. Sustained pain relief from 2 to 24 hours, will be assessed using the number of subjects that report a pain level of none or mild through the time period of interest.

9. Sustained pain relief from 2 to 48 hours, will be assessed using the number of subjects that report a pain level of none or mild through the time period of interest.

10. Freedom from MBS from 2 to 24 hours post-dose will be assessed using the number of evaluable subjects that report the absence of their MBS through the time period of interest.

11. Freedom from MBS from 2 to 48 hours post-dose will be assessed using the number of evaluable subjects that report the absence of their MBS through the time period of interest.

12. The proportion of subjects able to function normally from 2 to 24 hours post-dose, will be assessed using the number of subjects that self-report as "normal" on the FDS through the time period of interest.

13. The proportion of subjects able to function normally from 2 to 48 hours post-dose, will be assessed using the number of subjects that self-report as “normal” on the FDS through the time period of interest.

14. Time to rescue medication use up to 24 hours pose-dose

15. Time to first report of pain freedom up to 8 hours pose-dose

16. Time to first report of freedom from MBS up to 8 hours pose-dose

17. Time to first report of pain relief up to 8 hours pose-dose

18. Time to first report of absence of nausea up to 8 hours pose-dose

19. Time to first report of absence of photophobia up to 8 hours pose-dose

20. Time to first report of absence of phonophobia up to 8 hours pose-dose

21. Time to first report of return to normal functioning up to 8 hours post dose

5 Sample Size

If roughly 85% of the 715 subjects randomized to each treatment arm have a migraine in the allotted time period, there will be approximately 600 treated subjects per group.

Based on data from studies BHV3000-301 and BHV3000-302, 600 treated subjects provides 95% power to detect a difference between rimegepant and placebo on the subject’s self-reported most bothersome symptom. Also, 600 subjects provides 95% power to detect a difference in freedom from pain at 2 hours. Having at 95% power on each co-primary endpoint provides roughly 90% power to detect a difference on both endpoints jointly.

6 Analysis Sets

The following 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.

- Randomized subjects: Enrolled subjects who receive a randomization treatment assignment from the IWRS (rimegepant or placebo).

- Treated subjects: Enrolled subjects who take study therapy (rimegepant or placebo).

- Modified Intent to Treat (mITT) subjects: randomized subjects that take study therapy, have a migraine of moderate or severe intensity at the time of treatment, and provide at least one post-treatment efficacy data point.

No separate per protocol analysis set is defined for this study. There will not be any per protocol analysis conducted for this study.

7 Statistical Methods

7.1 General Statistical Considerations

All relevant data from all subjects entered into the database will be included in subject data listings. Unless specified otherwise, by-subject listings will be sorted by site, subject ID, and additional variables such as time points, as applicable. Listings will display site-subject ID and as randomized treatment group (as-treated treatment group for safety).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and other parameters by as-randomized treatment group (BHV3000, Placebo) and overall, unless specified otherwise. For safety analyses, tabulations will be produced by as-treated treatment group (BHV3000, Placebo) and overall, unless specified otherwise. For categorical variables, summary tabulations of the number and percentage of subjects within each category will be presented. If applicable, a category for missing data will also be presented. 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. The SD will be presented with the precision of the data + 2 decimal places. In general, the maximum number of decimal places reported should be 4 for any summary statistics.

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

Unscheduled or repeat assessments will not be included in summary tables unless specified otherwise, but will be included in listings.

For efficacy analyses, baseline is considered as the assessment at the onset of the treated migraine. Otherwise, baseline is the last non-missing assessment before or on the randomization date.

All statistical computations and construction of tables, listing and figures will be performed using SAS® Version 9.4 or later.

7.2 Adjusting of Covariates

The randomization is stratified by the use of prophylactic migraine medication (yes or no) and country (China and Korea). Hence, most analyses are stratified by the use or prophylactic medication and country.

7.3 Multiple Comparisons

Each co-primary endpoint will be tested for superiority to placebo at a two-sided alpha level of 0.05 without further adjustment for multiplicity. If the primary endpoint tests are both

significant, then the key secondary endpoints are evaluated using the procedure, conducted at alpha=0.05.

The Hochberg Procedure works as follows:

Step 1: Conduct all of your statistical tests and find the p-value for each test.

Step 2: Arrange the p-values in order from smallest to largest, assigning a rank to each one – the smallest p-value has a rank of 1, the next smallest has a rank of 2, etc.

Step 3: Calculate the Hochberg critical value for each p-value, using the formula (i/m)*Q, where:

i = rank of p-value

m = total number of tests

Q = your chosen false discovery rate

Suppose a 10% false discovery rate, with 5 tests, to calculate the Hochberg critical value for each p-value, we can use the following formula: (i/5)*0.1 where i = rank of p-value.

Step 4: Find the largest p-value that is less than the critical value. Designate every p-value that is smaller than this p-value to be significant.

7.4 Data Handling Conventions

7.4.1 Premature Withdrawal and Missing Data

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

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

For missing start date of AE or prior/concomitant medication, the following rules will be applied:

- If the start date is completely missing, the start date will be equal to the first dose date of study drug. However, if the stop date is not missing and is before the first dose date of study drug, then the stop date will be used instead.
- If the start day and month are missing and year is present, then the first day of the first month (January) will be used. However, if the year is the same as the year of first dose date, then the start date will be equal to the first dose date.
- If the start day is missing and year and month are present, the first day of that month will be used. However, if the year and month are the same as the year and month of first dose date, then the start date will be equal to the first dose date.

For missing stop date of AE or prior/concomitant medication, the following rules will be applied:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the date of completion/withdrawal, whichever is the latest. Otherwise, if the stop date is completely missing, it will not be imputed.
- If the stop day and month are missing and year is present, then the last day of the last month (December) will be used. However, if the year is the same as the year of date of completion/withdrawal, then the stop date will be equal to the date of completion/withdrawal.
- If the stop day is missing and year and month are present, the last day of that month will be used. However, if the year and month are the same as the year and month of date of completion/withdrawal, then the stop date will be equal to the date of completion/withdrawal.

These imputed dates will used to determine whether the AEs or medications are on-treatment.

7.4.2 Derived and Transformed Data

Calculation of Study Day

Study day describes the day of assessment/event date relative to the randomization date. It will be defined as:

- Date of assessment/event – randomization date + 1, if date of assessment/event is at or after randomization
- Date of assessment/event – randomization date, if date of assessment/event is prior to randomization

7.5 Study Subjects

7.5.1 Disposition of Subjects

A summary of subject disposition will be tabulated for all enrolled subjects by treatment group and overall. The disposition table will support the creation of a consort diagram. The categories in the table will include:

- Number of subjects screened
- Number of screen failed subjects and reason for screen failure
- Number of subjects randomized
- Number of subjects not treated, and the reasons for not being treated
- Number of subjects treated
- Completed Study
- Discontinued, and reasons for discontinuation
- Number of subjects in each analysis population

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

7.5.2 Protocol Deviations

The major protocol deviations will be tabulated by category based on randomized subjects. All major protocol deviations will be listed by subject based on medical review.

7.5.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by as-randomized treatment group and overall for the mITT population including: age, gender, childbearing potential for females, country, weight, height, body mass index (BMI), history of allergies (yes vs. no). A similar table will be made for the treated population by as-treated treatment group and overall to support safety.

A separate set of tabulation of demographic information will be made for subjects enrolled but not randomized (overall only) and subjects randomized but not treated (by as-randomized treatment group and overall).

The migraine history will be summarized by as-randomized treatment group and overall for the mITT population including but not limited to: age at migraine onset, experience migraines for at least one year prior to screening (yes vs. no), migraine history in years, duration of migraine attacks, number of moderate or severe migraines per month within last 3 months, use of prophylactic migraine medications (yes vs. no), primary migraine type. A similar table will be made for the treated population by as-treated treatment group and overall to support safety.

Demographic and baseline characteristics, and migraine history will be listed for all randomized subjects.

7.5.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later.

Based on the mITT population with as-randomized treatment group, the medical history data will be summarized with frequencies and percentages of subjects with at least one medical history, and subject frequencies and percentages on the System Organ Class (SOC) and Preferred Term (PT) levels. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. A similar table will be made for the treated population by as-treated treatment group and overall to support safety.

Medical history will be listed by subject.

7.5.5 Prior and Concomitant Therapies

Non-study medications will be coded into Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names using the World Health Organization (WHO) Drug <DDE (Enhanced) B3 Format, March 2020 or later>. For each subject, multiple records of the same medication will be counted only once within each ATC Level 2 and/or PT term.

The following non-study medications will be tabulated:

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 two subtypes:

- Prior 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 imputed stop date ≤ study drug start date – 1, or (2) imputed start date ≤ informed consent date ≤study drug start date –1 ≤ imputed stop date.
- Concomitant medications, defined as those taken on or after study drug, i.e., study drug start date ≤ imputed start or stop date.
- Prior prophylactic medications
- Current prophylactic medications
- Concomitant prophylactic medications

All prior, current and concomitant medications will be included in a listing. Additionally, non-drug therapies will be provided in a listing only.

7.5.6 Compliance

Considering the study drug will be administrated once for each subject, the treatment compliance will be not calculated and summarized.

The eDiary compliance at 2, 4, 6, 8, 24, and 48 hours post-dose by counting the number of subjects with missing data will be summarized using the mITT population.

7.6 Efficacy Analyses

Unless otherwise noted, all efficacy analyses will be conducted using the mITT population as outlined below. Efficacy tabulations will present results by as-randomized treatment group only (excluding overall), unless specified otherwise. All efficacy data will be included in listings by subject, treatment group, and time point (as applicable).

7.6.1 Primary Efficacy Analyses

The co-primary efficacy endpoints are pain freedom at 2 hours post-dose and freedom from MBS at 2 hours post-dose.

7.6.1.1 Pain Freedom at 2 Hours Post-Dose

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

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

The difference in percentage of pain freedom at 2 hours post dose between treatment groups is evaluated by computing the common risk difference, using Cochran-Mantel-Haenszel (CMH) weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no) and country (China or Korea). The risk difference is tested at a two-sided alpha level of 0.05. Missing data at 2 hours post-dose will be imputed as failures (i.e., non-Completers = Failure; NC=F). Subjects that use rescue medication prior to reporting pain freedom at 2 hours will be classified as failures (i.e., Rescue Medication = Failure; RM=F). If a stratum (prophylactic medication use: yes or no) has sparse data (less than 5 subjects), then the strata will be pooled.

A forest plot of the risk differences within each stratum, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq) will be provided.

Sensitivity analyses will be conducted as follows:

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

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

A sample SAS code for exact (Clopper-Pearson) 95% CIs is the following:

```
proc freq data=pain;
   by treatment pain_level;
   table response /  binomial (level="1" CL=(EXACT));
   weight count;
run;
```

A sample SAS code for common risk difference from Mantel Haenszel method is the following:

```
proc freq data=pain_2h;
   table prophylactic_migraine_medication*country*treatment*response /riskdiff (common
   CL=(WALD)) CMH ;
   weight count;
run;
```

7.6.1.2 Freedom from MBS at 2 Hours Post-Dose

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

A table showing descriptive statistics for the observed data, which includes the number and percentage of subjects reporting MBS present, MBS absent, MBS not reported and each of the migraine associated symptoms (phonophobia, photophobia or nausea) at baseline and

each post-dose timepoint by treatment group and overall. The table will include exact (Clopper-Pearson) 95% CIs for each percentage of MBS present/absent/not reported.

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

Sensitivity analyses will be conducted as follows:

1. The primary analysis is repeated, using the mITT population, with missing data at 2 hours post-dose imputed using LOCF. BOCF is permitted.

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

7.6.2 Key Secondary Efficacy Analyses

If the co-primary endpoint tests are both significant, then the key secondary endpoints are evaluated using the Hochberg Procedure. See Section 7.3 for details on the procedure.

7.6.2.1 Pain Relief at 2 Hours Post-Dose

Pain relief at 2 hours post-dose is assessed by tabulating the number of mITT subjects that report a pain level of none or mild (responses of 0 or 1 on the 4-point Likert scale) at 2 hours post-dose, by treatment group using the same methodology described in section 7.6.1.1.

Subjects with missing data at 2 hours post-dose will be imputed as failures (NC=F). Subjects that use rescue medication prior to reporting pain relief at 2 hours will be classified as failures (RM=F).

7.6.2.2 Function Normally at 2 Hours Post-Dose

Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions using a 4-point scale: Normal Function, Mild Impairment, Severe Impairment, or Required Bedrest. The proportion of mITT subjects who report "abnormal" at baseline and have a response of "normal" at the 2 hours post-dose will be evaluated using the same methodology described in section 7.6.1.1.

Subjects with missing data at 2 hours post-dose will be imputed as failures (NC=F). Subjects that use rescue medication prior to reporting function normality at 2 hours will be classified as failures (RM=F).

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

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

7.6.2.3 Use of Rescue Medication within 24 Hours

Whether or not a subject took rescue medication within 24 hours after the initial dose of study medication is tabulated by treatment group using mITT subjects, and the percentages are compared between treatment groups using the same methodology described in section 7.6.1.1.

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

7.6.2.4 Sustained Pain Freedom from 2 to 24 Hours

Sustained pain freedom is assessed using the number of mITT subjects that experienced no headache pain (response of 0 on Likert scale) at all time points from 2 through 24 hours post-dose. Subjects with missing pain scores at 1 or fewer time points, given that they have responses of no pain (response of 0 on 4-point Likert scale) at all other time points including the 2 and 24 hour post-dose time points, will be considered as successes. Subjects with responses missing at greater than 1 post-dose time point, missing data at the 2 or 24 hour time point (i.e. Non-Completers with more than 1 missing data point = Failure; NC1=F), or with any pain score greater than 0; or with any rescue medication within 24 hours (RM=F) will be considered as failures.

The proportion of mITT subjects who have a response of sustained pain freedom from 2 to 24 hours will be evaluated using the same methodology described in section 7.6.1.1.

7.6.2.5 Sustained Pain Freedom from 2 to 48 Hours

Sustained pain freedom is assessed using the number of mITT subjects that experienced no headache pain (response of 0 on Likert scale) at all time points from 2 through 48 hours post-dose. Subjects with missing pain scores at no more than 1 time point, given that they have responses of no pain (response of 0 on Likert scale) at the 2, 24, and 48 hour time points will be considered as successes. Subjects with responses missing at greater than 1 time point; missing data at the 2, 24, or 48 hour time point (NC1=F); or with any pain score greater than 0; or with any rescue medication within 48 hours (RM=F) will be considered as failures.

The proportion of mITT subjects who have a response of sustained pain freedom from 2 to 48 hours will be evaluated using the same methodology described in section 7.6.1.1.

7.6.3 Other Secondary Efficacy Analyses

7.6.3.1 Pain Freedom at 15, 30, 45, 60 and 90 Minutes

Pain freedom at 15, 30, 45, 60 and 90 minutes is assessed by tabulating the number of mITT subjects that report a pain level of none (responses of 0 on the 4-point Likert scale) at the specified post-dose time point, by treatment group. Subjects with missing data at the specified post-dose time point will be imputed as failures (NC=F). Subjects that use rescue medication prior to the specified post-dose time point will be classified as failures (RM=F).

The proportion of mITT subjects who have a response of pain freedom at the specified post-dose time point will be evaluated using the same methodology described in section 7.6.1.1.

7.6.3.2 Freedom from MBS at 15, 30, 45, 60 and 90 Minutes

Freedom from MBS at 15, 30, 45, 60 and 90 minutes post-dose is assessed by tabulating the number of mITT subjects that report an absence of their MBS (reported at migraine onset) at specified post-dose time point, by treatment group. Subjects with missing data at the specified post-dose time point will be imputed as failures (NC=F). Subjects that use rescue medication prior to the specified post-dose time point will be classified as failures (RM=F). Also taking IP prior to reporting the MBS, or failure to report a MBS are events that are imputed as treatment failures (IP=F).

The proportion of mITT subjects who have a response of MBS free at the specified post-dose time point will be evaluated using the same methodology described in section 7.6.1.1.

7.6.3.3 Pain Relapse from 2 to 48 Hours

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

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

The proportion of mITT subjects who have a response of pain relapse from 2 to 48 hours will be evaluated using the same methodology described in section 7.6.1.1.

7.6.4 Exploratory Efficacy Analyses

7.6.4.1 Binary Exploratory Endpoints

The binary exploratory endpoints will be evaluated using the same methodology described in section 7.6.1.1. The definitions of the binary exploratory endpoints are listed in the table 1 below.

Table 1 Definitions of the Binary Exploratory Endpoints

Endpoints	Definition of Success	Missing Data or Rescue Medication Handling
Pain Relief at 15, 30, 45, 60, and 90 minutes, 3, 4, 6, 8, 24, and 48 hours post-dose	Report a pain level of none or mild (responses of 0 or 1 on the 4-point Likert scale) at specified post-dose time point	NC=F; RM=F
Pain freedom at 3, 4, 6, 8, 24, and 48 hours post-dose	Report a pain level of none (responses of 0 on the 4-point Likert scale) at specified post-dose time point	NC=F; RM=F
Freedom from MBS at 3, 4, 6, 8, 24, and 48 hours post-dose	Report an absence of their MBS (reported at migraine onset) at specified post-dose time point	NC=F; RM=F; IP=F
Function normally at all post-dose timepoints except 2 hours	Subjects who report "abnormal" at baseline and have a response of "normal" at specified post-dose time point	NC=F; RM=F
Freedom from phonophobia at all post-dose time points	Subject who have phonophobia present at baseline and have absence of phonophobia at specified post-dose time point	NC=F; RM=F
Freedom from photophobia at all post-dose time points	Subject who have photophobia present at baseline and have absence of photophobia at specified post-dose time point	NC=F; RM=F
Freedom from nausea at all post-dose time points	Subjects who have nausea present at baseline and have absence of nausea at specified post-dose time point	NC=F; RM=F
Sustained pain relief from 2 to 24 hours	Subjects that experience no or mild headache pain (response of 0 or 1 on Likert scale) at all time points from 2 through 24 hours post-dose; Subjects with missing pain scores at 1 or fewer	NC1=F; RM=F

Endpoints	Definition of Success	Missing Data or Rescue Medication Handling
	time points, given that they have responses of no or mild pain (response of 0 or 1 on 4-point Likert scale) at all other time points including the 2 and 24 hour post-dose time points, will be considered as successes.	
Sustained pain relief from 2 to 48 hours	Subjects that experience no or mild headache pain (response of 0 or 1 on Likert scale) at all time points from 2 through 48 hours post-dose; Subjects with missing pain scores at 1 or fewer time points, given that they have responses of no or mild pain (response of 0 or 1 on 4-point Likert scale) at all other time points including the 2, 24 and 48 hour post-dose time points, will be considered as successes.	NC1=F; RM=F
Freedom from MBS from 2 to 24 hours post-dose	Subjects that experience freedom from their MBS at all time points from 2 through 24 hours post-dose; Subjects with missing MBS data at 1 or fewer time points, given that they have responses of freedom from MBS at all other time points including the 2 and 24 hour post-dose time points will be considered as successes.	NC1=F; RM=F; IP=F
Freedom from MBS from 2 to 48 hours post-dose	Subjects that experience freedom from their MBS at all time points from 2 through 48 hours post-dose; Subjects with missing MBS data at 1 or fewer time points, given that they have responses of freedom from MBS at all other time points including the 2, 24, and 48 hour post-dose time points will be considered as successes.	NC1=F; RM=F; IP=F

Endpoints	Definition of Success	Missing Data or Rescue Medication Handling
Function normally from 2 to 24 hours post-dose	Subjects that experience normal functioning on the FDS at all time points from 2 through 24 hours post-dose. Subjects with missing FDS scores at 1 or fewer time points, given that they have responses of normal at all other time points including the 2 and 24 hour post-dose time points will be considered as successes.	NC1=F; RM=F
Function normally from 2 to 48 hours post-dose	Subjects that experience normal functioning on the FDS at all time points from 2 through 24 hours post-dose. Subjects with missing FDS scores at 1 or fewer time points, given that they have responses of normal at all other time points including the 2, 24 and 48 hours post-dose time points will be considered as successes.	NC1=F; RM=F

7.6.4.2 Time to Event Endpoints

Time to First Use of Rescue Medication

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

Two tables will be created to support the plot. The first table presents the median time to rescue medication along with 95% CIs calculated using the method of Brookmeyer and Crowley and the log-rank p-value. The second table presents the number of subjects at risk, with an event, censored, and the survival probability estimate (with 95% CI) from the K-M product limit method for each period (e.g., 0-<2 hours, 2-<4 hours, …, 20-<22 hours, 22-24 hours) by treatment group.

Time to First Report of Pain Freedom, Pain Relief or Absence of Various Symptoms

For each of the following events, two sets of K-M plots and tables will be created:

- Time to first report of pain freedom up to 8 hours pose-dose
- Time to first report of freedom from MBS up to 8 hours pose-dose
- Time to first report of pain relief up to 8 hours pose-dose
- Time to first report of absence of nausea up to 8 hours pose-dose
- Time to first report of absence of photophobia up to 8 hours pose-dose
- Time to first report of absence of phonophobia up to 8 hours pose-dose
- Time to first report of return to normal functioning up to 8 hours post dose

For both sets of analyses, the analysis population for pain freedom, pain relief and MBS is the set of mITT subjects. The analysis population for nausea, phonophobia, and photophobia is the subset of mITT subjects that reported the symptom as present at the onset of their study migraine. The analysis population for functional disability is the subset of mITT subjects that reported abnormal functioning at the onset of their study migraine.

a) Actual Time for Event of Interest

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

b) Nominal Time for Event of Interest

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

7.7 Safety Analyses

Safety analyses will be conducted on the treated population by as-treated treatment group (i.e., the actual treatment received) and overall, unless otherwise specified.

7.7.1 Extent of Exposure

Extent of exposure is measured by subjects providing self-reported study drug exposure information in their eDiaries. As a check on this exposure data, study drug accountability data are provided by the study center on the “Study Drug Returned” CRF page. The self-reported study drug exposure data will be tabulated by treatment group and overall, for randomized subjects who had an on-study migraine, and will include:

- The number (and percentage) of randomized subjects that either took (correctly/incorrectly) or did not take study medication

  - The number and percentage who took the medication prior to providing baseline study migraine characteristics by counting the number of subjects who answered 'Yes' for question "Did you mistakenly take your study medication already?" in eDiary data.

  - The number and percentage that took study medication after providing baseline study migraine characteristics by counting the number of subjects who answered 'Yes' for question "Confirm you just took your Study Medication" in eDiary data.

  - The number and percentage of randomized subjects who reported not taking study medication by counting the number of subjects who answered 'No' both for questions "Did you mistakenly take your study medication already?" and "Confirm you just took your Study Medication" in eDiary data.

- The number and percentage of randomized subjects for whom no exposure data was reported

The study drug accountability will be tabulated by treatment group and overall, for randomized subjects who had an on-study migraine, and will include:

- The number and percentage of subjects with study drug returned and drug was not taken and the reason for drug not taken

- The number and percentage of subjects with study drug not returned and drug was taken

- The number and percentage of subjects with study drug not returned and drug was lost

A by-subject listing will be prepared that indicates the study drug exposure and accountability status of all randomized subjects.

7.7.2 Adverse Events

All Adverse Events (AEs) will be coded using the MedDRA version 23.0 or later. AEs toxicities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

All AEs will be summarized for the following categories: AEs with onset prior to randomization, AEs with onset on or after randomization but prior to study treatment, and treatment emergent adverse events (TEAEs) with onset on or after study treatment respectively.

An overall summary of AEs, which includes the number and percentage of subjects reporting any AEs, AEs with onset prior to randomization, AEs with onset on or after randomization but prior to study treatment, serious AEs with onset prior to randomization, serious AEs with onset on or after randomization but prior to study treatment, TEAEs, drug-related TEAEs, TEAEs with CTCAE grade ≥ 3, serious TEAEs, drug-related serious TEAEs, non-serious TEAEs, and TEAEs

leading to death will be presented. The number and percentage of subjects by SOC and PT will also be reported.

In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum NCI-CTC Grade (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) will be presented in the summary tables. A subject will be counted once at the highest grade for which the event occurred at the SOC level and the highest grade for each unique PT within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level. If CTCAE grade is missing for one event and the subject had no Grade ≥1 in the same category, "missing" row/column should be added in the summary tables with maximum CTCAE grade. The following summary tables will present the number and percentage of subjects by SOC, PT and maximum CTCAE grade.

- ◊ TEAEs
- ◊ Drug-related TEAEs

The following tables summarizing the number and percentage of subjects by SOC and PT will present only those TEAEs that occurred in at least 5% in at least one treatment group.

- ◊ TEAEs
- ◊ Drug-related TEAEs

All AEs will be included in listings. TEAEs are labelled in the listings. Listings will be provided for Serious Adverse Events (SAEs), AEs related to study drug, and grade >2 AEs separately. SAEs occurring in subjects enrolled but not treated will also be provided. AE leading to deaths will be listed for all enrolled subjects without regard to onset.

7.7.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations collected in a central lab include:

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count (WBC) with differential, platelets, lymphocytes count， neutrophils count and any other tests collected in the database.

Blood chemistry/electrolyte: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, CK. End of Treatment Visit - elevations in CK (>1.5xULN) may have further CK fractionation tests performed through the central lab.

Lipid panel: Cholesterol, LDL, HDL, triglycerides (Screening only).

Estimated glomerular filtration rate: eGFR using the estimated MDRD formula will be calculated and reported by the central lab at each visit that clinical laboratory tests are collected.

Urinalysis: pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose and blood. If blood, protein or leukocytes are positive, reflex to microscopic examination.

Urine Drug Screen: For drugs of abuse.

Clinical laboratory values will be expressed using International System of Units (SI). The observed value and change from baseline will be summarized for select continuous laboratory parameters at baseline and the end of treatment visit. In addition, the shift from baseline in laboratory tests will be summarized as the number and percentage of subjects in each category (low, within reference range, high) at baseline and the end of treatment visit. For AST and ALT, the shift tables will use the following categories: <=ULN, >ULN to <=3x ULN, >3x ULN to <= 5x ULN, >5x ULN to <= 10x ULN, >10x ULN to <=20x ULN and >20x ULN.

Clinically significant laboratory abnormalities will be identified according to the numeric laboratory test criteria in CTCAE Version 5.0, otherwise according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1. For the selected laboratory tests as following, the number and percentage of subjects by maximum CTCAE grade (0-4) will be presented for baseline period and on-treatment period. The number and percentage of subjects with indicated shifts in their maximum CTCAE grade from baseline to post-baseline will also be presented.

Hemoglobin, WBC, Lymphocytes Count, Neutrophils Count, platelets, ALT, AST, Total Bilirubin, Serum Creatinine, Sodium, Calcium, Potassium.

All central laboratory data and local laboratory data within scheduled visit windows due to restrictions of COVID-19 or other exceptional circumstances are also included in the summary analysis.

All laboratory data will be provided in by-subject listings that indicate which values are on study or on treatment. Additional listings will be presented for all abnormal laboratory values.

The local laboratory data collected in exceptional circumstances will be provided in a separate listing.

On-study laboratory values are those with collection date/time after the randomization date/time.

On-treatment laboratory values are those with collection date/time after the first dose of study drug date/time. (Thus, on-treatment laboratory values are a subset of on-study values.)

These definitions of on-study/on-treatment apply to vital signs, physical measurements, ECGs.

7.7.3.1 Liver Toxicity Evaluation

Potential drug induced liver injury (DILI) is those events meeting Hy's Law, defined as:

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

2. Total bilirubin (TBL) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase); and
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, included but not limited to: viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Any on-study potential DILI, meeting the above defined criteria, will be reported as SAEs in the SAE summary table (see Section 7.7.2). A by-subject listing of potential DILI will be prepared that shows the AT and TBL values for all subjects that experience either AT > 3 times the ULN or TBL > 2 times the ULN at any time.

Additionally, a table will be created that summarizes the on-study incidence (as the number and percentage of subjects with an elevation) of the following:

- >3x, >5x, >10x, and >20x ULN elevations of AST, ALT, and either ALT or AST
- Any elevations of bilirubin >1x ULN and >2x ULN
- Any elevations of ALP > 1.5x ULN
- Elevation of AST or ALT (>3x ULN) accompanied by elevated bilirubin (>1.5x ULN and >2x ULN)

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

7.7.4 12-Lead ECG

Each ECG parameter (heart rate, RR interval, PR interval, QT interval, QTcF interval and QRS duration) at baseline and the end of treatment visit, and the corresponding change from baseline will be summarized by treatment group and overall with descriptive statistics.

The shift tables with respect to normality of overall ECG assessment will be summarized. All 12-Lead ECG data will be listed.

7.7.5 Vital Signs

Each vital sign parameter (systolic blood pressure, diastolic blood pressure, sitting pulse rate, respiratory rate, heart rate, temperature and weight) at baseline and the end of treatment visit, and the corresponding change from baseline will be summarized by treatment group and overall with descriptive statistics. A by-subject listing of vital sign values will also be provided.

7.7.6 Physical Examination

All physical examination data for subjects with at least one clinically significant abnormal finding will be presented in a listing.

7.8 Pharmacokinetic Analyses

No pharmacokinetic data will be collected in this study.

7.9 Other Analyses

7.9.1 Subgroup Analyses

Subgroup analyses will be conducted for the co-primary endpoints and key secondary endpoints, unless otherwise noted. The baseline subgroup factors are defined as following.

Table 2. Definition of Subgroup Variables

	Subgroup Variable	Categories
Intrinsic Factors	Age Group	< 40, ≥ 40 years
	Gender	Male, Female
	Weight Group	Categorized as < median, ≥ median, where median is calculated overall across treatment groups combined for mITT subjects
Extrinsic Factors	Country	China, Korea
	Use of prophylactic migraine medications	Yes, No
	Baseline aura, defined as the aura status at onset of the treated migraine	Present, Absent

	Primary migraine type	Aura, Without Aura
	Number of moderate or severe migraines per month	Categorized as < median, ≥ median, where median is calculated overall across treatment groups combined for mITT subjects

7.9.2 COVID-19 Impact Analysis

A by-subject listing of COVID-19 visit impact will be provided for randomized subjects. The listing includes the following information: “what is the impact?”, “how is the impact related to COVID-19?”, and “Subjects discontinued study due to COVID-19?”.

7.10 Changes for Planned Analyses in Protocol

Not applicable.

8 References

Not applicable.

9 Tables, Figures and Listing Shells

Refer to attachment < BHV3000-310_TLF_MOCKS_v1.0.docx>.