A Multicenter, Open label, Long-term Safety Study of BHV3000 for the Acute Treatment of Migraine in Chinese Participants

BHV3000-318/C4591018

Final Analysis Plan

Version: 1.0

Date: April 07, 2024

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REVISION HISTORY

VERSION	VERSION DATE	AUTHOR	DESCRIPTION
1.0	07-Apr-2024	PPD	ORIGINAL VERSION

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Asparate Transaminase
ATC	Anatomical Therapeutic Chemical Classification of Drugs
BMI	Body Mass Index
BYOD	Bring Your Own Device
CGI-c	Clinical Global Impression-change
CI	Confidence Interval
CPK	Creatine Phospho Kinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
eDiary	Electronic Diary
eDISH	Drug-Induced Serious Hepatotoxicity
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
FUSS	Follow-up Safety Analysis Set
HbA1c	Hemoglobin A1c
LDH	Lactate Dehydrogenase
LTT	Long-Term Treatment
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MSQoLQ	Migraine-Specific Quality of Life Questionnaire
N	Number
NCI	National Cancer Institute
ODT	Orally Disintegrating Tablet
OP	Observation Period
PoM	Preference of Medication
PRN	Pro re nata
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SS	Safety Analysis Set

SBP	Systolic Blood Pressure
SD	Standard Deviation
SM	Satisfaction with Medication
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This Statistical Analysis Plan is based on the final study protocol BHV3000-318 (Protocol Version 5.0, dated 18Aug2023) and final case report form (CRF, Version 3.0, dated 21Mar2023). For the details for interim analysis, refer to Interim Analysis Plan (Version 1.0, dated 11Apr 2023).

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the long-term safety and tolerability of 75 mg Rimegepant ODT [dosed as needed (PRN)].

2.2 Secondary Objective

To evaluate the number of migraine days and severity of migraine attacks during long-term treatment (LTT) with 75 mg Rimegepant ODT (PRN) in participants compared to the observation period (OP).

2.3 Exploratory Objectives

- To evaluate the effect of 75 mg Rimegepant ODT treatment compared to baseline on the 14-Item Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQoLQ).
- To evaluate the effect of 75 mg Rimegepant ODT treatment on the Migraine Preference of Medication (PoM).
- To evaluate the effect of 75 mg Rimegepant ODT treatment on the Satisfaction with Medication (SM) survey.
- To evaluate the effect of 75 mg Rimegepant ODT treatment compared to baseline on the Migraine Disability Assessment (MIDAS).
- To evaluate the effect of 75 mg Rimegepant ODT treatment on the Clinical Global Impression-change (CGI-c) scale.

3 Study Design

3.1 Overall Design

This will be a multi-center, open-label, long-term safety study of BHV3000 for the treatment of acute migraine in Chinese participants to provide the long-term safety data in Chinese participants to bridge the existing comprehensive clinical trial data of 75 mg Rimegepant in migraine. Approximately 240 adult participants with migraine were planned to be enrolled to receive 75 mg of Rimegepant ODT (PRN use, up to 1 tablet per day).

The screening period will be consisted of a screening visit and a 30-day OP. Participants must have a history of 6 to 18 moderate to severe migraine attacks per month within 3 months prior to the Screening Visit in order to meet the entering criteria of this study.

Upon the completion of the screening visit, participants will be provided an electronic diary (eDiary) to document each day if a migraine occurs, the intensity of each migraine attack and

if the migraine is treated for the 30-day OP. Participants will record the standard of care migraine treatment received via bring your own device (BYOD). After completing the 30-day OP, the participant will return to the clinic with both records for the Baseline Visit. At the Baseline Visit, eligibility for continued participation in the study will be assessed, and eligibility will be determined as much as possible prior to dispensing study drug, participant need have least 6 migraine days during the 30-day OP to be eligible and women of childbearing potential (WOCBP) must have a negative pregnancy test result prior to dispensing study drug. After the investigator reviews the results of the baseline laboratory assessments and determines the participant's continued eligibility, the site staff will inform the participant whether or not he/she is eligible to start dosing in the LTT Phase. If eligible for the LTT, participants will be instructed that they can take study medication at the onset of a migraine (of mild to severe intensity). Participants will be instructed that they can take a maximum of one tablet of Rimegepant per calendar day during the 52-week LTT Phase at the onset of a migraine (of mild to severe intensity).

Participants are required to record their migraine occurrence and severity in the eDiary, to record all study medication doses via BYOD. Participants are also required to continue to record the standard of care migraine treatment taken via BYOD. Participants will also use BYOD to complete the PoM questionnaire and the SM questionnaire at specified study timepoints.

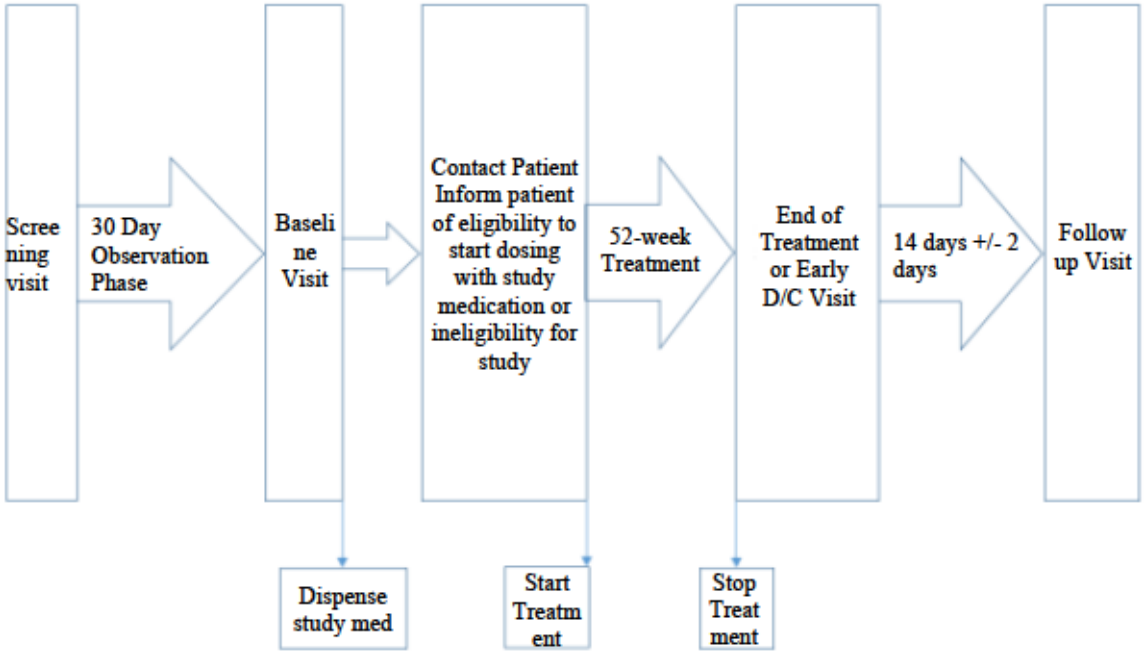
At selected study visits, participants will complete or will be administered the MSQoLQ v 2.1, the MIDAS, and CGI-c scale.

Procedures include study personnel review of the eDiary and BYOD with the participant, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). Study visits will be approximately every 4 weeks until Week 16 and then every 12 weeks for on-site visits + every 4 weeks phone calls in between every two on site visits until Week 52.

Participants will return to the study site at the end of Week 52 (± 7 days) for the End of Treatment Visit. There is a Follow-up Visit 14 days (± 2 days) after the Week 52/Early Termination Visit.

The overall study design schematic is shown in Figure 1.

Figure 1 Study Design



3.2 Randomization

Not applicable.

3.3 Blinding

This study is a single-arm trial. Blinding and unblinding methods are not applicable.

3.4 Sample Size Calculation

The sample size for this study is primarily based on historical data, considering the safety evaluation and estimation precision for the secondary endpoint. For the secondary endpoint of change from observation period in the number of migraine days per month from Week 9-12 in participants treated with rimegepant, data from previous long-term migraine study BHV3000-201 showed:

- 848 participants with a history of 6-18 days of migraine within 3 months prior to baseline.
- Mean (standard deviation, SD) baseline migraine days: 9.92 (3.09).
- Migraine days mean (SD) Weeks 9-12: 8.84 (4.97).
- Change from baseline in mean (SD) number of migraine days at weeks 9-12: -1.08 (4.74).

Based on the above historical trial data results and a t distribution assumption, in this single-arm study, 205 evaluable participants will provide a 90% power to observe a negative change from baseline in migraine days at Weeks 9-12 for a 1-sided 2.5% significance level, and finally 233 participants are required to be included considering 12% dropout rate based on BHV3000-201 trial. Considering other possible data loss, approximately 240 participants will be finally

enrolled.

In the case of 240 participants, if the adverse event rate is 5% and 1%, then the probability of observing at least one adverse event is >99.9% and 91.0%, respectively, thus providing sufficient information for safety and tolerability assessment after LTT with 75 mg rimegepant ODT in Chinese participants to bridge the available comprehensive clinical trial data of rimegepant 75 mg in the treatment of migraine.

4 Study Endpoints

4.1 Primary Endpoints

- Adverse events, common AEs (incidence ≥ 5%), serious adverse events (SAE), adverse events leading to study drug discontinuation, etc.; ECG, vital signs/physical measurements and clinical laboratory test abnormalities.

4.2 Secondary Endpoint

- Change from Observation Period in the number of migraine days by total and moderate or severe pain intensity for every 4-week interval and overall period during long-term treatment with 75 mg rimegepant ODT.

4.3 Exploratory Endpoints

- Change from baseline in results assessed with the 14-item MSQoLQ version 2.1 following treatment with 75 mg rimegepant ODT.
- Percentage of participants in each of 3 preference categories of the assessment with Migraine PoM for migraine following treatment with 75 mg rimegepant ODT.
- Percentage of participants in each of 7 satisfaction categories of the SM survey following treatment with 75 mg rimegepant ODT.
- Change from baseline in total score of the MIDAS following treatment with 75 mg rimegepant ODT.
- Percentage of participants in each of 7 categories of the CGI-c scale after treatment with 75 mg rimegepant ODT.

5 STUDY HYPOTHESIS

The statistical analysis is mainly descriptive, and no formal hypothesis testing will be performed.

6 ANALYSIS SETS

The following analysis sets will be determined-:

- Screened participants set: All participants who sign the informed consent. It will be used for the analysis of participant disposition.
- Enrolled participants set: Participants with an available date collected in the CRF on

which the investigator judges that they can be enrolled and notifies of their eligibility to start taking the investigational product by phone. It will be used for the analysis of participant disposition and drug accountability.

- Full analysis set (FAS): All participants who are enrolled and received at least one dose of the investigational product. It will be used for the analysis of baseline characteristics, as well as the analyses of exploratory endpoint measures.

- Efficacy analysis set (EAS): All participants in the FAS with≥ 14 eDiary days (not necessarily consecutive) in both the OP analysis period and ≥ 1 month (4-week interval) of the LTT analysis period. The EAS will be used to assess the secondary endpoint.

- Safety analysis set (SS): All participants who received at least one dose of investigational product. The SS will be used for safety analyses during treatment safety period.

- Follow-up safety analysis set (FUSS): All participants in the SS with last contact date (see Section 7.2.3) in the follow-up safety analysis period. The FUSS will be used for follow-up safety analyses.

7 STATISTICAL METHODOLOGY AND CONVENTIONS

7.1 General Methods

All relevant data of all participants entered into the database will be included in the participant data listings. Unless otherwise specified, participant listings will be ordered by site, participant ID, and other variables (e.g., time point). The listings will indicate the site-participant ID.

For categorical variables, a summary table of the number and percentage of participants in each category will be presented, and the category of missing data will be provided. For continuous variables, the descriptive statistics of n (e.g., number of participants), mean, median, SD, minimum, and maximum, etc. will be presented. The minimum and maximum values will be expressed with the same precision as the data. The mean and median values will be expressed with the data precision plus one decimal place. SD will be expressed with the data precision plus two decimal places. In general, all summary statistics will be reported with a maximum of four decimal places.

The 95% confidence interval (CIs) will be calculated for these endpoints: 1) Two-sided 95% CIs based on normal distribution will be calculated for continuous endpoints, including migraine days, MSQoLQ, and MIDAS. 2) Two-sided exact Clopper-Pearson CIs will be calculated for PoM, SM, and CGI-c.

For the safety data and the efficacy data collected in the CRF, unless otherwise specified, baseline will be the last non-missing assessment data prior to or on the day of first dose. For the efficacy data collected in the eDiary, baseline will be calculated based on the data from the observation analysis period.

SAS® (Version 9.4) will be used to perform all statistical calculations and generate tables, listings, and figures.

7.2 Data Processing Rules

7.2.1 Handling of Missing Data

Missing observed values

Unless otherwise specified, all data will be based on the actual measurement data.

Missing dates

For incomplete date data, the dates in the listings will be presented according to the actual situation.

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

- If the start date is completely missing, it will be imputed with the first dose date of study drug. However, if the end date is not missing and occurs prior to the first dose of study drug, the start date will be replaced with the earliest of non-missing end date or informed consent date.
- If the start month and day are missing but the start year is available, the start date will be imputed with the first day (Day 1) of the first month (January). However, if the year is the same as that of the first dose of study drug, the start date will be the same as the date of the first dose of study drug.
- If the start day is missing but the start year and month are available, the start date will be imputed with the first day (Day 1) of the month. However, if the start year and month are the same as those of the first dose of study drug, the start date will be the same as the date of the first dose of study drug.

If the end date of any AE or prior/concomitant medication is missing, the following rules will be applied:

- For AE if the end date is completely missing, the end date will be the latest of the participant withdrawal/completion date, death date, last active day of study drug, or start date. For prior/concomitant medication with completely missing end date and is no longer administered, the end date will be imputed following above rule for AE with completely missing end date. Otherwise, the end date will not be imputed.
- If the end month and day are missing but the end year is available, the end date will be imputed with the last day of the last month (December). However, if the end year is the same as that of the completion/withdrawal date, the end date will be the same as the date of completion/withdrawal.
- If the end day is missing but the end year and month are available, the end date will be imputed with the last day of the month. However, if the end year and month are the same as those of completion/withdrawal, the end date will be the same as the date of completion/withdrawal.

These imputed dates will be used to determine whether an AE or medication occurs (is used) during treatment.

7.2.2 Other Data Processing Rules

In the descriptive summaries of safety endpoints (e.g., absolute value and change from baseline in laboratory tests, vital signs, ECG), if an assessment is measured two or more times at a visit, then the last data of the visit will be used for analysis. The assessment results of all unscheduled and scheduled visits will be presented in the listings.

7.2.3 Derived Dates

Study Days

Refer to Protocol Section 4.3 for the schedule of assessments. Study Days are calculated from the LTT start date as follows:

- Assessment/event date/eDiary reference date – LTT start date + 1, if the assessment/event date ≥ LTT start Date;
- Assessment/event date/eDiary reference date – LTT start date, if the assessment/event date < LTT start Date, where

  LTT start date is defined as earlier of (1) Baseline Visit date, or (2) study drug start date (see also in Section 7.2.4).

Treatment Days

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

- Assessment/event date – study drug start date + 1, if the assessment/event date ≥ study drug start date.
- Assessment/event date – study drug start date, if the assessment/event date < study drug start date.

The Treatment Day will be displayed together with Study Day in the individual participants listings.

eDiary Days

An eDiary day is defined as a day with a complete eDiary reference date based on any question from the evening report headache log or follow up log (see step b.iv in Appendix: the derivation of migraine day).

Last Contact Date

The last contact date is used to determine select parameters (i.e., time on study, imputed non-study medication end dates), and is typically defined using non-imputed dates as follows:

1. Earliest complete death date from all sources that collect death dates (e.g., Death CRF), if it exists.
2. Otherwise, the maximum complete date of the following CRF or external data sources, as applicable: AE start or end; ECG; eDiary assessment; informed consent; laboratory test collection; non-study medication start or end; physical exam; protocol deviation;

questionnaire; rating scale; study intervention start or end; participant disposition completion/discontinuation; visit; vital signs.

7.2.4 Analysis Periods

To facilitate the analyses based on eDiary data (including eDiary compliance and migraine days), the analyses for safety endpoints, the following analysis periods will be defined.

Table 1. Analysis Periods

Analysis periods	Start date/time	End date/time	Usage
OP	Screening Visit date	LTT start date – 1 day	To be used to calculate the eDiary compliance, number of migraine days per 4 weeks in this period.
LTT	Earlier of (1) Baseline Visit date, and (2) study drug start date	Later of (1) Week 52/EOT date, and (2) study drug last dose date	To be used to calculate the eDiary compliance and number of migraine days per 4 weeks or the overall period in the long-term treatment.
Pre-treatment safety		Study drug start date – 1 day for AEs; study drug start date/time otherwise	To be used to assess the safety endpoints prior to study drug treatment.
Treatment safety	Study drug start date for AEs; after study drug start date/time otherwise	[Later of (1) Week 52/EOT date, and (2) study drug last dose date] + 7 days	To be used to assess the safety endpoints of the treatment period.
Follow-up safety	[Later of (1) Week 52/EOT date, and (2) study drug last dose date] + 8 days		To be used to assess the safety endpoints of the follow-up period.

7.2.5 Analysis Visit Windows

According to Section 4.3 of the protocol, the analysis visit windows for efficacy analyses will be defined. Analysis windows for the secondary endpoint will be defined within the OP and LTT analysis periods that are defined in Section 7.2.4 (See Table 2~~Table 2~~). The calculation of number of migraine days will be based on the study day as defined in Section **Error! Reference source not found.**~~7.2.3~~. Analysis windows for the exploratory endpoints will be defined directly as below in Table 3~~Table 3~~.

Table 2. Analysis Windows for Migraine Days

Per 4-week Interval	Analysis Window in the LTT Analysis Period (Study Day)
Month 1: Week 1 to Week 4	1-28

Month 2: Week 5 to Week 8	29-56
Month 3: Week 9 to Week 12	57-84
Month 4: Week 13 to Week 16	85-112
Month 5: Week 17 to Week 20	113-140
Month 6: Week 21 to Week 24	141-168
Month 7: Week 25 to Week 28	169-196
Month 8: Week 29 to Week 32	197-224
Month 9: Week 33 to Week 36	225-252
Month 10: Week 37 to Week 40	253-280
Month 11: Week 41 to Week 44	281-308
Month 12: Week 45 to Week 48	309-336
Month 13: Week 49 to Week 52	337-end of LTT

Table 3. Analysis Windows for MSQoLQ, MIDAS, PoM, SM, and CGI-c Scale

Scheduled Visits *	Target Day (Based on Study Day)	Analysis Window (Study Day)
Baseline	1	Prior to or on the first dose date
Week 12	84	71-98 #
Week 28	196	183-210 #
Week 40	280	267-294 #
Week 52	364	351- end of LTT
Early Termination	The Early Termination Visit or last post-baseline questionnaire from the early terminated participants	

* The PoM, SM, and CGI-c scale will not be collected at baseline, Week 12 and Week 40.
# For early terminated participants, the Week X window end date will be the minimum of (1) Early Termination Date -1 day or (2) Week X analysis window end date, where X is the last Week with Target Day being prior to Early Termination Date.

In Error! Reference source not found.~~Table 3~~, if there are multiple non-missing values fall into a same analysis window~~s~~, then the following algorithm will be taken to identify the value for analysis:

1. The value closest to the target day for the visit will be used.
2. If the observations are with equal distance from the target day in absolute value, the one with correct nominal visit label will be used. For example, if two observations fall into the analysis window for Week 28 Visit on Study Days 190 and 202, respectively, the observation that is recorded as Week 28 will be used.
3. If neither 1 nor 2 can identify the observation, then the last value measured is used.

All observations will, however, be included in the listings.

7.3 Study Participants

7.3.1 Participant Disposition

A participant disposition summary table will be provided based on screened participants. The following categories will be summarized in this table:

- Screened participants
- Screen failures and reasons for screen failure
- Enrolled participants
    - Treated participants
        - Participants who completed the treatment
        - Participants who discontinued treatment and reasons
        - Participants who completed the study
        - Participants who discontinued study and reasons
    - Untreated participants
- Not enrolled but treated

In addition, the number and percentage of participants in each analysis set will be summarized and listed based on screened participants.

7.3.2 Protocol Deviations

Based on the FAS, participants with important protocol deviations (PD) will be summarized according to the classification of PDs, with the number and percentage of cases calculated. Participants with PD will be listed in detail.

During the study conduct, PD reporting was updated per TigerMed's latest SOP. PD categories were changed from Major/Minor PDs to Important/Non-important PDs. The previous major PD categories will be converted to Important PD categories based on medical review. For the minor PDs, if the PDs were due to COVID-19, the categories of these minor PDs will be converted to non-important PD categories based on medical review; if the PDs were not due to COVID-19, minor PD categories will be kept and will not be converted to non-important PD categories. Important PDs and PDs due to COVID-19 will be summarized based on the new PD categories. Listings of PDs will be provided with the new PD categories (Important/Non-important) and the previous PD categories (Major/Minor). See Appendix: Mapping Rule of PD Categories.

The details and severity of PDs will be eventually determined at the data review meeting before database lock.

7.3.3 Demographics/Baseline Characteristics

The demographics and baseline characteristics will be descriptively summarized based on the FAS using the method described in Section 7.1, including:

- Age, gender, ethnicity, weight (kg), height (cm), body mass index (BMI; kg/m^2), and

history of allergy (yes, no).

Age at informed consent will be calculated. Age (in years) and BMI will be summarized as a continuous variable, and by categories with numbers and percentages. Age will be categorized as <65 vs. ≥65. BMI will be categorized as < 25 vs. ≥25 to <30 vs. ≥ 30.

The demographics and baseline characteristics will be listed.

7.3.4 Migraine History

The migraine history will be descriptively summarized according to the method described in Section 7.1 and be listed based on the FAS, including:

- Age at migraine onset, did the participant experience migraines for at least one year prior to screening (yes vs no), migraine history (years), average duration of untreated migraine attacks (hours), number of moderate to severe migraines per month within last 3 months, primary migraine type (migraine with or without aura), migraine symptoms (headache attacks lasting 4-72 hours, unilateral location, pulsating quality, moderate or severe pain intensity, experience nauseas and/or vomiting during headache, experience photophobia and/or phonophobia during headache), Aura symptoms (visual, sensory, speech and/or language, motor, brainstem, retinal, other symptoms).

7.3.5 Medical History

The medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA Version 25.0).

The number and percentage of participants with at least one medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the FAS. For each participant, multiple medical histories of the same SOC or PT will be counted only once within each SOC and PT. Tables will be presented in descending order based on frequency of each SOC, and then in descending order based on frequency of each PT within a SOC.

Medical histories will be listed by participants.

7.3.6 Prior and Concomitant Medications

Summaries will be performed based on the SS.

Non-study drugs will be coded into Anatomical Therapeutic Chemical Classification System (ATC) codes and preferred drug names using the World Health Organization Drug Dictionary (WHO-DD). For multiple records of the same drug taken by a participant, the drug will be counted only once under each ATC Grade 2 term and/or PT item.

The non-study medication types include:

- Prior medications, including previous and current medications

  Prior medications are defined as those taken before study drug, i.e., imputed start or end date < study drug start date. Note that all non-study medications are considered prior for participants with missing study drug start date. Prior medications include the

following subtypes:

- Previous medications, defined as those taken before informed consent, i.e., those with an imputed start or end date < informed consent date.
- Current medications, defined as those taken on or after informed consent and before study drug.

- Concomitant medications, defined as those taken with study drug.

Summaries will be provided for: current prophylactic migraine medications, concomitant prophylactic migraine medications, current medications, and concomitant medications, respectively.

All non-study previous, current, and concomitant medications, including prophylactic migraine medications and other medications, will be listed.

7.3.7 Prior and Concomitant Non-drug Therapies

Non-drug therapies will be categorized into previous, current, and concomitant therapies based on therapy start/end dates using the same criteria as stated in Section 7.3.6 and be summarized using the same method as stated in Section 7.3.6.

A detailed listing of non-drug therapies will be provided based on the SS.

7.3.8 Drug Accountability and eDiary Compliance

The drug accountability will be summarized by the following categories based on the enrolled participants using the method described in Section 7.1:

- At least one kit dispensed
- Did not return any drug
- Ever lost or wasted drugs
- Average number of dispensed tablets (tablets per month) = 4 (weeks)* (sum of total number of dispensed amount - amount dispensed on the latest return date) / ((latest return date – earliest dispense date) /7)
- Average number of returned tablets (tablets per month) = 4 (weeks)* sum of total number of returned amount / ((latest return date – earliest dispense date) /7)
- Average number of tablets lost or wasted (tablets per month) = 4 (weeks)* sum of total number of not used and not returned amount / ((latest return date – earliest dispense date) /7)

Drug distribution and return profiles will be listed.

The compliance of eDiary Migraine records will be summarized by OP and LTT analysis period based on the SS using the following formula:

Compliance in each period = (actual number of eDiary entry days in the period/ number of days in the period) * 100%, where number of days in the period = analysis period end date – analysis period start date + 1 day (see Section 7.2.4).

- The compliance will be summarized using the method described in Section 7.1.
- The number and percentage of participants with ≥ 80%, ≥ 90% compliance will also be calculated.

A listing of the compliance will be provided.

7.4 Efficacy Analyses

Efficacy analyses will be based on the FAS, unless specified otherwise. Summaries will be based on the analysis visit windows (refer to Section 7.2.5.).

7.4.1 Efficacy Analysis of the Secondary Endpoint

The number of migraine days (refer to appendix: the derivation of migraine day) by total and severity of migraine attacks will be calculated for the OP and the overall LTT period as defined in Table 1~~Table 1~~, and each month (i.e., 4-week interval) as defined in Table 2~~Table 2~~.

Analyses will be based on the EAS, ie, participants who have ≥ 14 eDiary days (not necessarily consecutive) within both the OP analysis period and at least one month (4-week interval) in the LTT analysis period. For the assessment timepoints, all values observed after taking standard of care migraine medications (acute or prophylactic) will be used.

The number of migraine days in OP, per 4-week in LTT period, and overall LTT period will be prorated to 28 days to account for days with missing migraine data:

Number of migraine days in the OP

= 28*(sum of migraine days in the observation analysis period) / (sum of eDiary days in the observation analysis period).

Number of migraine days per month (4-week interval) in the LTT period

= 28*(sum of migraine days within a 4-week interval) / (sum of eDiary days within this 4-week interval).

Overall LTT

= 28*(sum of migraine days in the LTT analysis period) / (sum of eDiary days in the LTT analysis period.

Note that, in the above calculations, participants must have ⩾14 days of eDiary data (not necessarily consecutive) in the OP, each month (4-week interval) in the LTT period; all participants in EAS will be included in the calculation for overall LTT period.

Prorated absolute values (based on above formulas), change and percentage change from OP in migraine days per month (4-week interval) of LTT period and overall LTT period will be summarized descriptively by severity (total; moderate or severe) using the statistics mentioned

in Section 7.1. For the analysis of the percentage change from OP, only participants who have at least one migraine day (absolute, not prorated to 28 days) of appropriate severity in the OP will be included.

In addition, for each 4-week interval in the LTT period, the number and percentage of participants with the migraine days decreased by ≥ 25%, ≥ 30%, ≥ 50%, and ≥ 60% from the OP will be summarized by severity. The number and percentage of participants with the mean number of migraine days in the overall LTT period decreased by ≥ 25%, ≥ 30%, ≥ 50%, and ≥ 60% from the OP will be summarized by severity.

Longitudinal plots will display the mean reduction in the number of migraine days in the LTT period from the OP on the Y-axis and LTT month on the X-axis, by severity. Vertical bars will display 95% CI. Longitudinal plots for the mean number of migraine days in the LTT period will also be displayed using the same format.

The number of migraine days in prorated absolute value, change from OP, percentage change from OP, and percentage reduction categories will be listed.

7.4.2 Efficacy Analysis of the Exploratory Endpoints

Definitions and analysis methods for the exploratory endpoints are introduced in this section.

Tables will display results by analysis visit window as defined in Section 7.2.5.

Migraine-Specific Quality of Life Questionnaire (MSQoLQ) V2.1

This questionnaire has 14 items and 3 domains (Restrictive Role Function, Preventive Role Function, and Emotional Function), among which Restrictive Role Function consists of 7 items, Preventive Role Function consists of 4 items, and Emotional Function consists of 3 items. A 6-point scale is adopted for the answer options to each item, with 1 indicating the quality of life is not damaged ("Never") and 6 indicating maximum damage ("All the time"). First, individual item scores are recoded as {7 – original item score}. Next, the sum of the questionnaire results of all recoded items in each domain will be calculated and used as the raw score. If in a particular domain, the questionnaire results of less than or equal to half of the items are missing (e.g., the questionnaire results of ≤ 3 Restrictive Role Function items, ≤ 2 Preventive Role Function items are missing, or ≤ 1 Emotional Function item are missing). The raw score of the domain will be imputed as the mean of the questionnaire results of non-missing items. If in a particular domain, the questionnaire results of more than half of the items are missing, the raw score of the domain will be regarded as missing. And then, the raw score of each domain will be transformed into a score in the 0-100 scale. Each domain will be analyzed based on the transformed raw score.

The transforming rules are shown in the figure below:

Domain	Raw score transforming rule
Restrictive Role Function	(Raw score - 7) *100/35
Preventive Role Function	(Raw score - 4) *100/20
Emotional Function	(Raw score - 3) *100/15

The transformed raw score and change from baseline for each domain will be presented by visit

and domain, with n, mean, SD, maximum, minimum, median, and 95% CI as described in Section 7.1.

A listing of original item scores and transformed scores for each domain from the MSQoL questionnaire will be provided.

Migraine Preference of Medication Questionnaire (PoM)

PoM is a 5-item rating scale used to record participants' perception of whether the study drug they are taking is more beneficial in treating their pain compared with prior medication. The statistical analysis will be based on 3 categories, as shown in the figure below:

Item	Category
I feel much better, and I prefer this drug	Preference for study drug
Slightly better than the prior medication	Preference for study drug
Basically the same as the prior medication	No preference
Slightly worse than the prior medication	Preference for prior medication
I feel much worse, and I prefer my prior medication	Preference for prior medication

The number and percentage of participants in each category will be summarized by visit. The calculation of percentage will be based on participants with PoM data by visit, and the two-sided exact Clopper-Pearson 95% CI will be calculated as described in Section 7.1.

A listing of Preference of Medication (PoM)- will be provided.

Satisfaction with Medication Questionnaire (SM)

The SM questionnaire is a 7-item rating scale used to record whether participants are satisfied with their headache medication. The number and percentage of participants in each category will be summarized by visit. The calculation of percentage will be based on participants with SM data by visit, and the two-sided exact Clopper-Pearson 95% CI will be calculated as described in Section 7.1.

A ~~lisring~~ listing of Satisfaction with Medication (SM) Survey will be provided.

Migraine Disability Assessment Questionnaire (MIDAS)

The MIDAS questionnaire is a retrospective participant self-report scale consisting of 5 questions, which is used to measure disability related to headache, such as time lost due to headache caused by paid work or school, housework, and non-working activities. The value and change from baseline in the total score will be presented by visit, with n, mean, SD, maximum, minimum, median and 95% CI as described in Section 7.1.

The total score is calculated as the sum of item scores to all 5 questions.

A listing of individual item score, and the calculated total score will be provided.

Clinical Global Impression-change (CGI-c) scale

The CGI-c scale is a 7-item observer-rated scale used to assess the global improvement in

participants. The number and percentage of participants in each category will be summarized by visit. The calculation of percentage will be based on participants with CGI-c data by visit, and the two-sided exact Clopper-Pearson 95% CI will be calculated.

A listing of individual item responses will be provided.

7.5 Safety Analyses

Safety analyses during the pre-treatment, treatment safety analysis periods will be summarized based on the SS. Safety analyses for follow-up safety period will be summarized based on FUSS.

7.5.1 Drug Exposure

Drug administration data collected via CRF will be used to summarize drug exposure as follows:

- Time in the OP (weeks) = (OP end date – OP start date + 1)/7
- Time in the LTT period (weeks) = (LTT analysis period end date – LTT analysis period start date + 1)/7
- Time on rimegepant exposure (weeks) = (study drug end date – study drug start date + 1)/7
- Cumulative administered rimegepant dose (tablets) = sum of doses administered on the drug management page of CRF.
- Average administered rimegepant dose during the LTT period (tablets per month) = 4 (weeks)*cumulative administered dose (tablets) / Time in the LTT period (weeks) if time in the LTT period ≥ 2 weeks; = cumulative administered dose if time in the LTT period < 2 weeks.

In the above drug exposure summary, descriptive statistics of n, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be presented.

- For the average rimegepant exposure during the LTT period (tablets per month), the number and percentage of participants will be summarized by < 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month.
- The number and percentage of participants taking > 1 tablet per day (i.e., actual dose of "other"). It will be calculated based on the study drug administration CRF.

In addition, rimegepant exposure during the LTT period will be summarized by the average Rimegepant exposure categories and total for each month (i.e., 4-week interval) as defined in Table 2~~Table 2~~. The rimegepant exposure (tablets) for each month will be determined as follows:

- rimegepant exposure (tablets) for Month X = sum of doses administered on the drug management page of CRF within the Month X window, where X=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12.

- rimegepant exposure (tablets) for Month 13 = sum of doses administered on the drug management page of CRF within the Month 13 window if exposure ≤28 days; = sum of doses administered on the drug management page of CRF within the Month 13 window *28/exposure days if exposure >28 days.

Participant's exposure to the study drug will be listed in detail.

7.5.2 Adverse Events

The AEs will be coded by the latest version of MedDRA. The toxicity of AEs will be graded using National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) v5.0.

All AEs will be categorized according to the safety analysis periods (refer to Section 7.2.4), ie. pre-treatment safety period, treatment safety period, and follow-up safety period:

- Pre-treatment AEs, ie, those with imputed AE onset dates falling within the pre-treatment safety period.
- Treatment-emergent adverse event (TEAEs), ie, those with imputed AE onset dates falling within the treatment safety period. See Section 7.2.1 for AE onset date imputation.
- Follow-up AEs, i.e., those with imputed AE onset dates falling within the follow-up safety period.

Drug-related AEs are the AEs assessed by the site investigator as having a relationship to the investigational product of "definitely related", "probably related", or "possibly related".

An overall summary of AEs will display the number and percentage of participants reporting the following AEs for participants in different categories of average rimegepant exposure (< 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month) and overall participants for treatment safety and follow-up safety analysis periods, respectively, as below:

- For treatment safety analysis period, the following will be summarized using SS:
  - Any TEAE, any drug-related TEAE,
  - Any serious TEAE, any drug-related serious TEAE,
  - Any TEAE with CTCAE grade ≥ 3, any drug-related TEAE with CTCAE grade ≥ 3,
  - Any TEAE leading to drug interruption; any drug-related TEAE leading to drug interruption,
  - Any TEAE leading to treatment discontinuation, any drug- related TEAE leading to treatment discontinuation,
  - Any TEAE leading to study discontinuation, any drug-related TEAE leading to study discontinuation,
  - Any TEAE leading to death, any drug-related TEAE leading to death.

- For follow-up safety analysis period, the following will be summarized using FUSS:
    - Any AE,
    - Any SAE,
    - Any AE leading to death.

Further, the number and percentage of participants with the following AEs will be tabulated by SOC and PT for participants in different categories of average rimegepant exposure < 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month) and overall participants for treatment safety and follow-up safety analysis periods, respectively, as below:

- For treatment safety analysis period, the following will be summarized using SS:
    - TEAEs,
    - Drug-related TEAEs,
    - Serious TEAEs,
    - Drug-related serious TEAEs.
- For follow-up safety analysis period, the following categories will be summarized using FUSS:
    - AEs,
    - Serious AEs.

In addition, the number and percentage of participants with the following AEs will be tabulated by SOC, PT, and maximum CTCAE grade (Grade 1, 2, 3, 4, 5, ≥ 3, ≥ 4) for participants in different categories of average rimegepant exposure (< 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month) and overall participants for treatment safety and follow-up safety analysis periods, respectively, as below:

- For treatment safety analysis period, the following will be summarized using SS:
    - TEAEs,
    - Drug-related TEAEs.
- For follow-up safety analysis period, the following categories will be summarized using FUSS:
    - AEs.

For the above AE tables that display CTCAE toxicity grade, if the same AE is reported by the same participant repeatedly, the AE with the highest NCI-CTC grade (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing) will be presented in the summary table. The participants will be counted once according to the highest grade under each unique PT item in the SOC.

Participants reporting the following AEs will be listed separately using SS:

- AEs with CTCAE Grade ≥3,
- AEs leading to treatment discontinuation,
- AEs leading to study discontinuation,
- AEs leading to death,
- AEs Leading to drug Interruption.

All AEs will be listed by participant ID with a flag indicating each AE to be a pre-treatment AE, a TEAE, or a follow-up AE.

A death listing for all the screened participants will be generated.

7.5.3 Clinical Laboratory Tests

The clinical laboratory evaluation results collected by the central laboratory will include:

(1) Clinical safety laboratory tests

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell counts with differential count, and platelets.

Chemistry: sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c, BUN (urea), serum creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, creatine phosphokinase (CPK) (with fractionation test, if CK result is > 1.5 × ULN), estimated glomerular filtration rate (eGFR) using the estimated modification of diet in renal disease (MDRD) formula (calculated at central lab), aspartate transaminase (AST), alanine transaminase (ALT), Alkaline Phosphatase (ALP) and Bilirubin (Total, Direct, Indirect).

(2) Blood lipid test: cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride.

(3) Urinalysis: pH, specific gravity, ketones, nitrite, urobilinogen, leukocyte esterase, protein, glucose, and occult blood. Microscopic examination will be performed if occult blood, protein or white blood cells are positive.

(4) FSH: for WOCBP at screening visit to determine WOCBP status.

Results from central and local laboratory tests will be summarized. For local laboratory parameters with different units from the central laboratory, the results will be converted. Results cannot be converted will be included in the listing.

For the continuous hematology, chemistry, and blood lipid laboratory test parameters, observed values and changes from baseline will be summarized at the following timepoints: baseline, each scheduled visit, early termination, and Follow-up visit using the SS.

Summaries will be performed using central laboratory results if both central and local laboratory parameters are collected at a visit. If there are multiple values collected at the same

visit, rule stated in Section 7.2.2 will be applied.

The number and percentage of participants with laboratory test abnormalities according to CTCAE grade (Grade 0; Grade 1-2; Grade 3-4) will be presented during the treatment (using SS) and follow-up (using FUSS) safety analysis periods, respectively. The highest CTCAE grade during the analysis period will be used. Additionally, the abnormal laboratory tests in at least 5% of overall participants or CTCAE Grade 3-4 will be summarized by average rimegepant exposure (< 2, ≥ 2 to < 8, ≥ 8 < 14, <14, ≥ 14 tablets per month, and overall).

The number and percentage of participants with shifts from baselines in CTCAE grades (Grade 0, 1, 2, 3, 4, 1-4) to the treatment safety period based on SS (refer to Section 7.2.4) will also be presented, using the highest CTCAE grade.

The number and percentage of participants with LFT elevations in the following categories will be presented during the treatment based on SS safety analysis period, for participants in different categories of average rimegepant exposure (< 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month) and overall participants:

- Cumulative elevations

ALT > 1x, > 3x, > 5x, > 10x, and > 20x ULN

AST > 1x, > 3x, > 5x, > 10x, and > 20x ULN

ALT or AST > 1x, > 3x, > 5x, > 10x, and > 20x ULN

TBL > 1x and > 2x ULN

ALP > 1.5x ULN

These are based on the highest ratio of value to ULN for each laboratory test. Note that participants may be in > 1 category for each laboratory test.

- Mutually exclusive elevations

ALT > ULN to ≤ 3x ULN, > 3x ULN to ⩽ 5x ULN, > 5x ULN to ≤ 10x ULN, > 10x

ULN to ≤ 20x ULN, and > 20x ULN

AST > ULN to ≤ 3x ULN, > 3x ULN to ⩽ 5x ULN, > 5x ULN to ≤ 10x ULN, > 10x

ULN to ≤ 20x ULN, and > 20x ULN

These are based on the highest ratio of value to ULN for each laboratory test. Note that participants may be in only 1 category for each laboratory test.

- Composite elevations

ALT or AST > 3x ULN and TBL > 1.5x ULN. This is based on the highest ratio of value to ULN for each laboratory test.

ALT or AST > 3x ULN and TBL > 2x ULN. This is based on the highest ratio of value to

ULN for each laboratory test.

The number and percentage of participants with shifts in LFT elevations from baseline to the treatment safety period using SS (refer to Section 7.2.4) will also be presented according to the greatest elevation; categories for ALT and AST are ≤ ULN, > ULN to ≤ 3 × ULN, > 3 × ULN to ≤ 5 × ULN, > 5 × ULN to ≤ 10 × ULN, > 10 × ULN to ≤ 20 × ULN, and > 20 × ULN.

All laboratory data will be listed using SS. For a given graded laboratory test, the listing displays all test results over time for participants with a CTCAE Grade 3 to 4 laboratory test abnormality at any time point. For a given pregnancy test, the listing also displays all test results over time for participants with a positive pregnancy test result at any time point, defined as a serum or urine pregnancy test with "positive" character value.

The scatter plot of evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) during the study using SS will display the maximum ratio of total bilirubin level divided by ULN on the y-axis versus the maximum ratio of ALT level divided by ULN on the x-axis, where the maxima are in the same study period but not necessarily concurrent. Both axes are on the $\log_{10}$ scale with minima of 0.1. Ratios < 0.1x ULN are set to 0.1. A horizontal reference line is placed at 2x ULN, and a vertical reference line is placed at 3x ULN. The lower left quadrant is labeled "Normal Range", the upper left quadrant is labeled "Hyperbilirubinemia", the lower right quadrant is labeled "Temple's Corollary", and the upper right quadrant is labeled "Possible Hy's Law Range." A footnote specifies that "Ratios < 0.1x ULN are set to 0.1." and is displayed only if ≥ 1 participant has a ratio set to 0.1.

7.5.4 Vital Signs and Physical Measurements

For each vital sign parameter (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature) and physical measurement parameter (weight, BMI), observed values and changes from baseline will be summarized at the following timepoints: baseline, each scheduled visit, early termination, and Follow-up visit using SS. See Section 7.2.2 for handing multiple values in an analysis window.

The number and percentage of participants with vital sign abnormalities in the following categories will be presented during the treatment (using SS) and follow-up (using FUSS) safety analysis periods, respectively, for participants in different categories of average rimegepant exposure (< 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month) and overall participants:

Individual listing will be provided using SS.

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg)	max. >140	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg)	max. >90	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Pulse rate (beats/min)	min. <40	max. >120

7.5.5 12-lead ECG

For each 12-lead ECG parameter (heart rate, PR interval, QRS duration, QT interval, and QTcF), the observed values and changes from baseline will be summarized at the following timepoints: baseline, each scheduled visit, early termination, and Follow-up visit using SS. See Section 7.2.2 for handing multiple values in an analysis window.

The number and percentage of participants with ECG abnormalities in the following categories will be presented during the treatment safety (using SS) and follow-up (using FUSS) safety analysis periods, respectively, for participants in different categories of average rimegepant exposure (< 2, ≥ 2 to < 8, ≥ 8 < 14, <14 and ≥ 14 tablets per month) and overall participants:

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

Individual listing will be provided using SS.

7.6 COVID-19-related Visit Impact

A listing of enrolled participants with visits impacted by COVID-19 will be provided. The listing will contain the following information: "What was the impact?", "How was the impact related to COVID-19?", and "Did the participant withdraw from the study due to COVID-19?".

8 APPENDIX

8.1 The Derivation of Migraine Day

Migraine Day Derivation

eDiary logs with all evening questions and follow-up questions being empty will be deleted.

A migraine day is defined as an eDiary day with either (I) or (II):

I. Qualified migraine headache based on all the following criteria (a and b):

a. Lasting for ≥ 30 minutes:

i. Headache duration

= (1) Headache end time# – headache start time#, where headache start and end dates (with "ENDED" to the question about headache status) are the same, and eDiary entry date is on the same date;

= (2) Headache end time# – headache start time#, where headache start and end dates (with "ENDED" to the question about headache status) are the same, but eDiary entry date is later than the headache start date;

= (3) Headache end time# – 0 o'clock of the headache end date, where headache end date (with "ENDED" to the question about headache status) is later than the

headache start date, and eDiary entry date is later than the headache start date but could be either equal to or later than the headache end date.

= (4) Headache end time# – 0 o'clock of the headache end date, where headache start date is missing, headache end date (with "ENDED" to the question about headache status) is available and eDiary entry date is either equal to or later than the headache end date, and follow-up log is not available.

ii. Headache-to-entry duration

= (1) eDiary entry time# – headache start time#, where headache start and eDiary entry dates are the same, and headache end time# is missing (not answered or "STILL CONTINUING" to the question about headache status);

= (2) eDiary entry time# – 0 o'clock of the entry date, where eDiary entry date is later than the headache start date, and headache end time# is missing (not answered or "STILL CONTINUING" to the question about headache status).

iii. Headache-to-FU duration

= follow-up log headache end time@ or follow-up log entry time@ – headache start time#, where follow-up headache log is available with a headache end time or a follow-up log entry time if headache end time is missing.

iv. For participants who have a headache occurrence lasting for >1 calendar day such that ≥1 evening logs are recorded on consecutive eDiary entry days with the same occurrence start time and headache end time being missing (i.e. "STILL CONTINUING" status) for earlier days and non-missing (i.e. "ENDED" status) for the last day, duplicate the evening log that is(entered after headache start date) and (the log prior to this log does not have a same headache start date). Calculate the following duration for the duplicated evening log,

Headache-to-midnight duration

= midnight of the day - headache start time#.

That is, for examples below, participant 2 log 2 and participant 3 log 2 will each be split into 2 logs:

for participant 2, log 2 will be split into an added log with headache starting from 19AUG2022:21:10:00 to midnight (i.e., duration in iv) and an original log with headache starting from 0'clock to entry time of 20AUG2022:19:54:51 [i.e. duration in ii (2)];

for participant 3, log 2 will be split into an added log with headache starting from 17MAR2023:17:30:00 to midnight (i.e., duration in iv) and an original log with headache starting from 0'clock to 18MAR2023:21:00:00 [i.e. duration in i (3)].

Participant ID	Log	eDiary Entry Time	Headache (YES/NO)	Headache Start Time	Headache End Time	Headache Status

1	1	23SEP2022:21:54:22	YES	23SEP2022:18:33:00		STILL CONTINUING
1	2	24SEP2022:22:38:17	YES	23SEP2022:18:33:00		STILL CONTINUING
1	3	25SEP2022:22:57:30	YES	23SEP2022:18:33:00	25SEP2022:08:22:00	ENDED
2	1	19AUG2022:19:19:29	No			
2	**2**	**20AUG2022:19:54:51**	**YES**	**19AUG2022:21:10:00**		**STILL CONTINUING**
2	3	21AUG2022:18:16:40	YES	19AUG2022:21:10:00	20AUG2022:15:15:00	ENDED
3	1	16MAR2023:19:47:45	YES	16MAR2023:11:00:00	16MAR2023:19:48:00	ENDED
3	**2**	**18MAR2023:21:28:57**	**YES**	**17MAR2023:17:30:00**	**18MAR2023:21:00:00**	**ENDED**

v. A log is considered as lasting for ≥ 30 minutes if the response to question about headache lasting ≥ 30 minutes is "YES", or any of the durations calculated in i, ii, iii is ≥ 30 minutes; and a duplicated evening log is considered as lasting for ≥ 30 minutes if duration calculated in iv is ≥ 30 minutes.

vi. Define an eDiary reference date to be the eDiary entry date for scenarios i (1), ii (1), ii (2), and headache start date for scenarios i (2), iii, iv, and headache end date for scenario i (3) and i (4) . A migraine day will be identified based on the eDiary reference date.

b. Meeting at least one of the following criteria (i or ii):

i. ≥ 2 of the following pain features based on "yes" response to questions with the same eDiary reference date/time:

- Unilateral location#,
- Pulsating quality (throbbing)#,
- Moderate or severe pain intensity#
- Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)#

ii. ≥ 1 of the following associated symptoms based on "yes" response to questions with the same eDiary reference date/time:

- Nausea#
- Vomiting#
- Both photophobia# and phonophobia#

II. Taking triptan, ergotamine or study medication: "Yes" response to the question about taking triptan to treat headache or during aura #@, question about taking ergotamine to treat headache or during aura #@, or question about taking study medication to treat headache or during aura #@& in the LTT analysis period.

Note that data marked with "#" are identified from the evening headache log; data marked with "@" are identified from the follow-up headache log; data marked with "&" are identified from drug administration information collected via CRF.

III. After a migraine day is derived based on steps I and II for each log, the logs with duplicated eDiary reference date will be deduped by keeping the original log if both original log and added log are on the same reference date, followed by keeping the one with migraine day identification=YES, next followed by keeping the most severe migraine, and then followed by keeping the log with the latest headache end date.

8.2 The Mapping Rule for PD Categories

During the BHV3000-318 (C4951018) study, the protocol deviation categorization form and record form were updated due to changes in the Tigermed SOP and as per the Pfizer requirements. The updated document became effective in the system on 27 July 2023. The new categorization form has made some changes to the PD categorizations compared to the old version, which includes assigning PDs into more refined sub-categories, and modifying the PD severity criteria. For example, before the update, the categories were labeled A, B, C… J, with corresponding sub-categories were A1, A2, A3, A4, B1, B2, and so on; after the update, the categories were changed to 1), 2), 3)... 9), and there are several sub-categories under each category; the severity levels would be Major/Minor before the update, and were updated to Important/Non-important. Since the PD data in the old and new versions of the categorization forms may not correspond to each other or cannot be directly converted between each other, PDs are presented in two different fashions in the current PD log. In order to present a consistent PD categorization in the final CSR, the following decision was made upon discussion within the study team from Pfizer and Tigermed:

According to the regulatory requirements and the Pfizer and Tigermed SOPs, analysis on Important PDs would be presented in the CSR body. Since the definitions and criteria for Important PD in the old version are generally consistent with those for Major PD in the new version, with the only difference lying in that the same PD would be categorized into different categories in the two versions, it is possible to convert a Major PD into an Important PD following consistent rules, as well as converting a COVID-19-related Minor PDs into Non-important PDs.

The recommended rules for mapping the old categorization of Major PDs to the new categorization of Important PDs are as follows:

- The original A2 "Subject has signed ICF, but did not sign the updated ICF and continued in the trial" corresponds to 11) -10 "ICF signed by the subject or subject's legal representative is a superseded or outdated version (the PD will be regarded as Important if the updated ICF contains updated or important information on risk-related language)".

- The original A4 "Informed consent process or ICF completion, management or other aspects did not meet requirements" corresponds to 11) -7 "Updated ICF was not signed

at the first visit after EC approval (the PD will be regarded as Important if the updated ICF contains updated or important information on risk-related language)".

- The original B2 "Subject met exclusion criteria, but entered the study" corresponds to 1) -2 "Subject met exclusion criteria, but entered the study".

- The original C2 "Study drug dose error (refer to protocol 7.2.2 and 7.2.3") corresponds to 2) -2 "Error in study drug dose or method of administration, etc. (refer to protocol 7.2.2 and 7.2.3)".

- The original C4 "Study drug was not stored or transported per protocol, and was administered to the subject before it was assessed as usable by the sponsor" corresponds to 2) -4 "Study drug storage issues (e.g., if subject was dispensed and used study drug with temperature excursions that has been deemed not usable or has not be confirmed as whether or not usable, it would be regarded as an Important PD. If subject was dispensed study drug with temperature excursions but did not use it, or used it after it was confirmed to be further usable, it would be regarded as a Non-important PD".

- The original D1 "Subject used protocol-prohibited medications or therapies during the trial" corresponds to 3) -1 "Subject used protocol-prohibited medications or therapies".

- The original E1 "Pregnancy test (if applicable) missing" corresponds to 4) -3 "Pregnancy test missing".

- The original E2 "Subject entered study despite missing laboratory assessments or auxiliary examinations, etc., concerning the eligibility criteria" corresponds to 6) -3 "Study procedure or examination missing or incomplete (for indicators concerning the assessment of eligibility criteria or primary endpoint, if the procedure/examination has had an important impact on study results, e.g., where the procedure/examination was missing for more than 12 consecutive weeks, it would be regarded as Important)".

- The original E5 "eDiary or BYOD not completed per protocol (to be assessed as Major in case of eDiary missing for 6 or more times a month)" corresponds to 6) -2. The original E6 corresponds to 6) -5 if with the keywords "contraception" or "pregnancy" in the PD description, or to 6) -2 "study procedure or examination (eDiary completion, ECG, physical examination, questionnaire, rating scale, etc.) not done per protocol" if without the above key words. The original F2 "Visit missing" corresponds to 5) -2 "Visit missing (to be regarded as Important if the missing visit has had an important impact on study results, e.g., leading to safety data missing for more than 12 weeks or withdrawal from visit)".

- The original J1 "Not fitting into any of the above categories" corresponds to 10) -1 "No standard sub-categories".

The recommended rules for mapping the of categorization of Minor PDs due to COVID-19

to the new categorization of Non-Important PDs due to COVID-19 are as follows:

- The original F1 "Visit out of allowable window" corresponds to 5) -1 "Visit not performed per protocol (visit out of window)".

- The original F2 "Visit missing" corresponds to 5) -2 "Visit missing (to be regarded as Important if the missing visit has had an important impact on study results, e.g., leading to safety data missing for more than 12 weeks or withdrawal from visit)".

- The original E-3 "Other laboratory tests, physical examination, vital signs, questionnaire, or other protocol-specified procedures missing" corresponds to 6) -3 "Study procedure or examination missing or incomplete (for indicators concerning the assessment of eligibility criteria or primary endpoint, if the procedure/examination has had an important impact on study results, e.g., where the procedure/examination was missing for more than 12 consecutive weeks, it would be regarded as Important)" if with the keyword "vital signs" in the PD description, or to 4) -4 "Lab test not done (for indicators concerning the assessment of eligibility criteria or primary endpoint, if the test has had an important impact on study results, e.g., where the test was missing for more than 12 consecutive weeks, it would be regarded as Important)" if without the above keyword.

- The original E-4 "Lab test or other procedure out of protocol-specified window" corresponds to 6) -2 "study procedure or examination (eDiary completion, ECG, physical examination, questionnaire, rating scale, etc.) not done per protocol".

- The original E-6 "Laboratory test, contraceptive measure or other procedure not done per protocol or Lab Manual " corresponds to 4) -4 "Lab test not done (for indicators concerning the assessment of eligibility criteria or primary endpoint, if the test has had an important impact on study results, e.g., where the test was missing for more than 12 consecutive weeks, it would be regarded as Important)" if with the keyword "bicarbonate" in the PD description; or to 6) -2 "study procedure or examination (eDiary completion, ECG, physical examination, questionnaire, rating scale, etc.) not done per protocol" if with the keyword "liver function"; or to 4) -7 "Laboratory test process did not meet prescribed conditions (including subject's state at blood collection and specimen handling, etc.) but specimen was analyzed" if with the keyword "transport"; or to 5) -1 "Visit not performed per protocol (visit out of window)" if without the above keywords.

Once mapped into the corresponding new categories, all Major PDs will be summarized as Important PDs, and all (Minor) PDs due to COVID-19 will be summarized as (Non-important) PDs due to COVID-19 in the CSR. The above is hereby specified.

9 REFERENCES

Guidelines on the Planning and Reporting of Drug Clinical Data Management and Statistical

Analysis (Attachment of 2016 No.113 Announcement)

Guideline on Biostatistics in Clinical Trials (Attachment of 2016 No.93 Announcement)