PROTOCOL TITLE: A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine

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Biohaven Pharmaceuticals

Protocol BHV3500-202

A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine

Statistical Analysis Plan

Version 6.0

Date: 07-Feb-2022

SIGNATURE PAGE

Protocol Title: A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine

Sponsor: Biohaven Pharmaceuticals, Inc

Document Version: 6.0

Date: 07-Feb-2022

Author: PPD PPD PPD
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Signature:_____

Date:_____

Sponsor Approval

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

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

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

Sponsor Signatories:

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REVISION HISTORY

Version	Description of Change
1.0	Original issue based on Protocol Version 2.0 (10-Jul-2020)
2.0	Based on Protocol Version 2.0 (10-Jul-2020). Sections 6.4.1, 6.4.1.1, and 6.4.1.3: Changed "associated with" to "related to". Section 7.1: Modified the derivation of the LTT end date/time. Section 9.1.5.1: Changed the visit impact characteristic code abbreviation of "A" to "N" (typo), and updated the examples. Section 9.1.5.2: Updated footnotes to describe the abbreviations in the COVID-19 visit impact code.
3.0	Based on Protocol Version 2.0 (10-Jul-2020). General: Applied standards from the Biohaven Style Guide. Abbreviations: Added CK. Replaced CV with CYP3A4. Section 3.2: Specified data sources for endpoints. Section 3.2.1: In Table 1, specified the analysis set in the "Summary" row instead of "Endpoint" row. Section 3.2.3: In Table 2, specified the analysis set in the "Summary" row instead of "Endpoint" row, and replaced the outcomes research analysis set with the safety analysis set. Sections 4.1 and 6.2.5: Removed the outcomes research analysis set. Section 6.2.3: Specified linkage to the AE CRF and display of reasons for not completing milestones. Moved text to new subsections 6.2.3.1 through 6.2.3.5. Added IWRS LTT enrollment date to the listing. Section 6.2.6.3: Specified that the "ongoing" category exists only before the final database lock. Added "(including the follow-up visit)" to the end of the study completion question. Section 6.2.5: Specified the meaning of "last" for deriving baseline, and that the baseline value of a parameter is independent of the baseline analysis visit in Table 3. Section 6.2.6.3: Specified linkage to medical history and AE CRFs. Section 6.4: Referenced the Zavegepant Core SAP about slotting safety parameters into analysis periods. Section 6.4.1: Added a reference to exposure-adjusted multiple occurrences of unique AEs in the Zavegepant Core SAP. Renumbered subsections. Section 6.4.1.1: New section "Deaths". Added a table of deaths. Specified the contents of the deaths listing. Section 6.4.1.2: Removed death from the AE overview table. Section 6.4.1.4: Changed "in ≥ X% of subjects" to "with ≥ X% frequency". Removed 2 tables of exposure-adjusted AEs. Added 4 tables of exposure-adjusted multiple occurrences of unique AEs. Section 6.4.2: Added a listing of local laboratory CK fractionation. Section 6.4.5: Simplified the description of the S-STS. Section 6.5: Replaced the outcomes research analysis set with the safety analysis set Section 7.1: Modified the derivation of the last contact date.

Version	Description of Change
	Section 7.2: Specified that all measurements are pre-treatment for subjects in the enrolled analysis set with missing study drug start date, and all measurements are pre-LTT for subjects in the enrolled analysis set with missing LTT start date. Section 7.3: Modified Table 3: changed the Week 2 analysis visit window; modified the third column header; and deleted footnote1. Specified that the baseline analysis visit in Table 3 is independent of the baseline value of a parameter in Section 6.2.5. Section 9.1.1: Changed the visit impact characteristic code abbreviation of "A" to "N" (typo). Section 9.2: Added select CYP3A4 inducers and inhibitors.
4.0	Based on Protocol Version 2.0 (10-Jul-2020). Signature page: Replaced PPD with PPD Abbreviations: Added HDL, LDL, and CTMS. Removed MOH. General: Spelled out MOH. Renamed "IWRS LTT enrollment date/time" to "IWRS baseline visit date" throughout". Section 2.4: Specified that SAP Versions 2.0, 3.0, and 4.0 are based on Protocol Version 2.0. Section 4.3: Added the number of total treated migraine days per month in the overall LTT. Section 6.1.1.2: Specified that the listing of significant protocol deviations displays analysis period, study day, and treatment day. Section 6.2.2: Changed "LTT participated" to "full". Section 6.2.3: Removed text about displaying reasons for not completing milestones, and added a reference to the Zavegepant Core SAP. Modified the contents of the subject disposition listing. Sections 6.2.3 and 6.2.3.1: Replaced 'Inclusion/Exclusion Findings Summary CRF' with 'Inclusion/Exclusion Criteria CRF'. Section 6.2.4.1: New section "Relevant Protocol Deviations". Moved text from Section 6.2.4 here. Section 6.2.4.2: New section "Significant Protocol Deviations". Added a listing of significant protocol deviations. Section 6.4: Identified which safety listings display COVID-19 visit impact code for visits that are impacted by COVID-19 throughout. Section 6.4.2: Clarified the visit schedule for serum chemistry. Changed "local laboratory CK fractionation" to "CK elevation questionnaire". Section 6.4.2.1: Specified that results for grade 3 to 4 laboratory test abnormalities support the primary objective. Section 6.4.2.2: Changed "Section 6.5" to "Section 6.4.6". Moved the definition of treated migraine day to Section 6.4.6. Removed "average". Section 6.4.6: Moved the definition of treated migraine day from Section 6.4.2.2. Section 6.4.6.1: New section "Migraine Days per Month over Time". Moved text describing output here. Changed "decrease" to "reduction", and "intensity" to "migraine intensity". Modified reduction categories. Replaced histograms with longitudinal plots. Section 6.4.6.2: New section "Treated Migraine Days per Month". Added tables of treated migraine days. Section 6.4.7: Added pre-treatment SAEs for subjects treated with zavegepant in studies BHV3500-201/301. Section 6.5: Specified that the COVID-19 visit impact code is displayed in all listings except for PoM and SM. Section 7.1: Modified the derivations of study drug date/time and last contact date.

Version	Description of Change
	Section 8: Specified that all TLFs described in this SAP are produced for the interim and final CSRs. Section 9.2: • Replaced deviation for previous enrollment in study BHV3500-202 with LTT participated or treated with study drug more than once and assigned > 1 subject identifier. • Removed deviations for elevated HbA1c, systolic blood pressure, and diastolic blood pressure during pre-LTT. • Replaced "at any time during the study" or "any time during the study" with "on or after informed consent" throughout. • Added divalproex as a prohibited non-study medication.
5.0	Based on Protocol Version 2.0 (10-Jul-2020). Section 6.2.5: Removed reference to the central laboratory. Specified to see Sections 6.4.2.3, 6.4.3.1, 6.4.4.1, and 6.5 for handling of ties on the same measurement date or time. Section 6.2.6.1: Modified derivation of average zavegepant exposure (sprays per month). Modified example on exposure categories. Replaced 'study drug' with 'zavegepant'. Specified that the analysis for the eDiary zavegepant sprays per month over time is based on absolute spray counts per month with an example provided; and is followed by the calculation of the LTT period. Section 6.2.6.3: Replaced 'CRGP' with 'CGRP'. Section 6.4: Modified algorithm for selecting a safety parameter value for an analysis visit window. Section 6.4.2: Specified that laboratory tests are analyzed using results from the external central laboratory CCI which identifies expired kits, and from local laboratory tests reported on CRFs. Specified that the central laboratory reports both laboratory collection date and time, whereas the CRFs only capture laboratory collection date. Modified the contents of laboratory listings to identify expired kits from the central laboratory. Section: 6.4.2.3: Modified algorithm for selecting a laboratory test value for an analysis visit window. Defined a viable laboratory test value as those from (1) kits from the central laboratory that are not expired or (2) local laboratory tests reported on CRFs. Section 6.4.3: Specified that all parameters are reported with measurement date only (no time). Section 6.4.3.1: Specified the handling of ties on the same measurement date. Section 6.4.4: Specified that ECGs are measured with both acquisition date and time by the external source CCI Section 6.4.4.1: Specified the handling of ties on the same acquisition date and time. Section 6.5: Modified algorithm for selecting an outcomes research measurement for an analysis visit window.
6.0	Based on Protocol Version 2.0 (10-Jul-2020). Signature page: Replaced PPD with PPD Section 2.4: Specified that SAP Versions 5.0 and 6.0 are based on Protocol Version 2.0. Section 4.3: Changed reference from Section 6.4.6 to Section 6.4.6.2. Section 6.2.5.4: Modified the definition of non-study pre-LTT medications. Section 6.2.6.1: Modified exposure categories for eDiary zavegepant exposure and LTT exposure. Section 6.4.6.2: Modified derivation of treated migraine days per month and categories.

Version	Description of Change
	Section 8: Specified that all TLFs described in this SAP are produced for the interim CSR, except those for the migraine analysis set, exploratory endpoint of migraine days per month, and the subgroup of total treated migraine days per month in the overall LTT.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Blood urine nitrogen
CGI-c	Clinical Global Impression - change
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CK	Creatine kinase
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CSR	Clinical study report
CTMS	Clinical trial management system
CYP3A4	Cytochrome P450 3A4
ECG	Electrocardiogram
eDiary	Electronic diary
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
HDL	High-density lipoprotein
IP	Investigational product
IWRS	Interactive web response system
LDL	Low-density lipoprotein
LFT	Liver function test
LTT	Long-term treatment
MDRD	Modification of Diet in Renal Disease
MIDAS	Migraine Disability Assessment
MSQ	Migraine Specific Quality of Life Questionnaire
OP	Observation phase
PID	Patient identifier

Abbreviation	Definition
PoM	Preference of medication
PT	Preferred term
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SM	Satisfaction with Medication
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
TLF	Table listing figure
ULN	Upper limit of normal

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3500-202: A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine.

This SAP contains the analysis details and methodology to answer the study objectives, including planned tables, listings, and figures (TLFs), which provide the basis for the results section of the clinical study report (CSR).

1.1 Research Hypothesis

Zavegepant is safe and well tolerated in the treatment of migraine.

1.2 Schedule of Analyses

During the course of this study, safety and exposure data are monitored on an ongoing basis. Interim analyses may be conducted after an interim database lock that is prior to last patient last visit. The CSR is produced after the last patient last visit and final database lock. All analyses described in this SAP are performed after the final database lock.

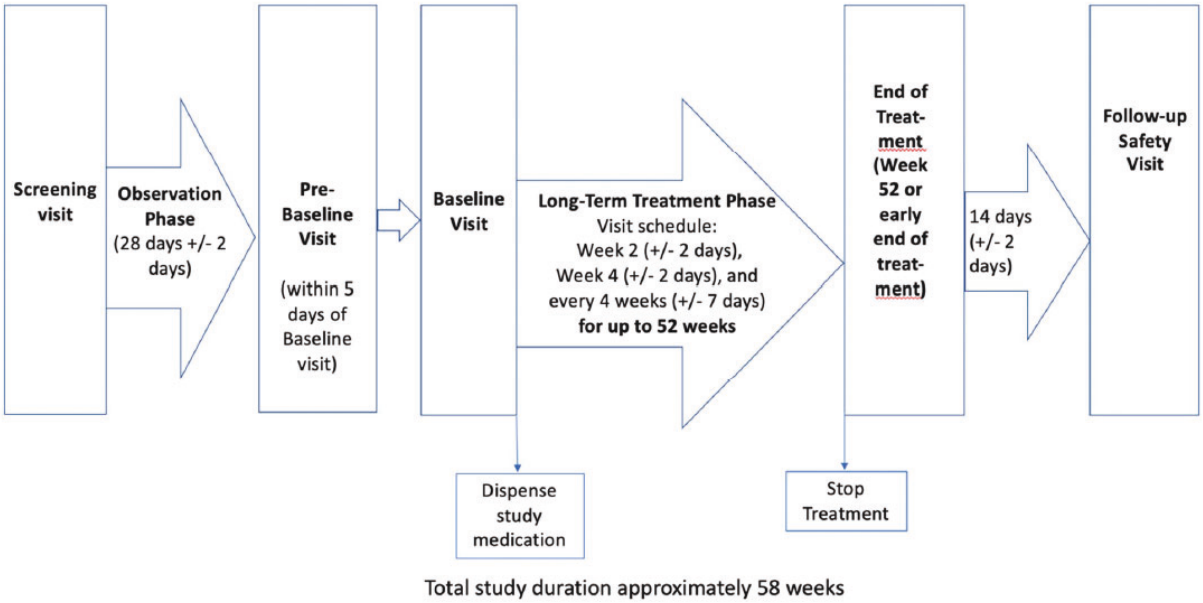
2 STUDY DESCRIPTION

2.1 Study Design

This is a multi-center, open-label study to assess the safety and tolerability of long-term use of IN zavegepant, taken up to 8 times per month (every 28 days) in subjects with migraine. The study drug, zavegepant (BHV-3500), is formulated as a 10 mg IN dose and is administered using an Aptar Unit Dose System (UDS) liquid spray device. Each UDS device contains a single dose of study drug zavegepant. The subjects are instructed to take their study drug, when they have a migraine headache, up to 8 times per month.

The design of the study is shown in Figure 1. The study screens approximately 800 subjects to treat approximately 600 subjects. After completion of screening procedures and a 28-day observation phase (OP), eligible subjects may participate in the study up to 52 weeks in the long-term treatment (LTT) phase. Study visits are roughly every 2 weeks during the first month and then every 4 weeks until Week 52 in the LTT phase. Subjects who complete or discontinue early from LTT phase also complete a follow-up visit approximately 14 days after the End of Treatment (EOT) visit.

Figure 1: Study Schematic



2.2 Treatment Assignment

The Interactive Web Response System (IWRS) assigns a subject identifier number at the screening visit.

If the subject is deemed eligible to participate in the study at the baseline visit, then the IWRS assigns specific container numbers for all open-label study drug to be dispensed at the baseline visit and subsequent visits in the LTT phase.

2.3 Blinding and Unblinding

This is an open-label study. All TLFs produced before or after data base lock are produced with the actual treatment group.

2.4 Protocol and Protocol Amendments

BHV3500-202 SAP Versions 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0 are based on BHV3500-202 Protocol Version 2.0.

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objective

To evaluate the safety and tolerability of zavegepant.

3.1.2 Secondary Objectives

Not applicable.

3.1.3 Exploratory Objectives

1. To evaluate the frequency of adverse events (AEs) potentially associated with drug abuse.
2. To evaluate frequency of AEs indicating medication-overuse headache.
3. To evaluate the frequency and intensity of hepatic-related AEs.
4. To evaluate the frequency of liver function test (LFT) elevations (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]) based on fold changes above the upper limit of normal (ULN).
5. To evaluate the frequency of ALT or AST > 3x ULN concurrent with TBL > 2x ULN.
6. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.
7. To evaluate Sheehan-Suicidality Tracking Scale (S-STS) scores and changes from baseline.
8. To evaluate the frequency of nasal edema and inflammation from nasal inspection.
9. To evaluate the reduction from the OP in the number of migraine days per month by intensity.
10. To evaluate Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQ) domain scores and changes from baseline.
11. To evaluate Preference of Medication (PoM).
12. To evaluate Satisfaction with Medication (SM).
13. To evaluate Migraine Disability Assessment (MIDAS) scores and changes from baseline.
14. To evaluate Clinical Global Impression - change (CGI-c).

3.2 Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The 4 attributes of an estimand include the population of interest, endpoint of interest, summary of the endpoint, and specification of how intercurrent events are reflected in the scientific question of interest.

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

Intercurrent Events

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation. Study drug discontinuation before the time point of interest defining the endpoint is considered an intercurrent event.

- For safety objectives, study drug discontinuation is handled with a "while-on-treatment strategy," i.e., response to treatment prior to the occurrence of the intercurrent event of interest, such that all observed values of the endpoint of interest are used prior to study drug discontinuation.
- For outcomes research and other objectives, study drug discontinuation is handled with a "treatment policy strategy", i.e., the occurrence of the intercurrent event is considered irrelevant, such that all observed values of the endpoint of interest are used regardless of study drug discontinuation.

Refer to Section 4.1 for analysis sets that are used to assess endpoints.

Data Sources for Endpoints

AEs are from AE case report forms (CRFs).

Laboratory test results are from an external central laboratory and local laboratory test CRFs.

Migraine days per month, PoM categories, and SM categories are derived from subject-reported electronic diary (eDiary) data.

S-STS scores, MSQ scores, MIDAS scores, and CGI-c categories are derived from their respective CRFs.

3.2.1 Primary Objective Estimand

The estimand attributes corresponding to the primary endpoint for this study are shown in Table 1.

Table 1: Primary Objective Estimands

Objective	**Safety and tolerability**
Safety Endpoint	Number and percentage of subjects with AEs occurring in ≥ 5% of treated subjects by intensity, SAEs, AEs leading to study drug discontinuation, and clinically significant laboratory abnormalities on treatment. The frequency of AEs is based on the number and percentage of subjects with events. The frequency of clinically significant laboratory test abnormalities is determined from grade 3 to 4 laboratory tests, and based on the number and percentage of subjects with abnormalities among those with laboratory test data.
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

3.2.2 Secondary Objective Estimands

Not applicable.

3.2.3 Exploratory Objective Estimands

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

Table 2: Exploratory Objective Estimands

Objective	**Frequency of AEs potentially associated with drug abuse**
Safety Endpoint	Number and percentage of subjects with AEs potentially associated with drug abuse
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of AEs indicating medication-overuse headache**
Safety Endpoint	Number and percentage of subjects with AEs indicating medication-overuse headache
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency and intensity of hepatic-related AEs**
Safety Endpoint	Number and percentage of subjects with hepatic-related AEs by intensity
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of LFT elevations based on fold changes above ULN**
Safety Endpoint	Number and percentage of subjects with LFT elevations (ALT, AST, ALP or TBL) based on fold changes above ULN on treatment
Summary	Frequency for the safety analysis set with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN**
Safety Endpoint	Number and percentage of subjects with ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN on treatment
Summary	Frequency for the safety analysis set with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of ALT or AST > 3x ULN in temporal association with AEs**
Safety Endpoint	Number and percentage of subjects with ALT or AST > 3x ULN concurrent with nausea, vomiting, anorexia, abdominal pain or fatigue on treatment
Summary	Frequency for the safety analysis set with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy

Objective	**S-STS scores and changes from baseline**
Safety Endpoint	For the ideation subscale, behavior subscale, and total scores: • Worst (highest) score on-treatment and follow-up • Change from baseline to worst score on-treatment and follow-up • Number and percentage of subjects in each of 5 worst change from baseline score categories (< -1, -1, no change, 1, > 1) on-treatment and follow-up
Summary	Summary statistics and frequency for the safety analysis set with S-STS data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Frequency of nasal edema and inflammation from nasal inspection**
Safety Endpoint	Number and percentage of subjects with local irritation AEs
Summary	Frequency for the safety analysis set
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
Objective	**Reduction from the OP in the number of migraine days per month by intensity**
Safety Endpoint	Values and changes from OP in the number of migraine days per month during LTT (1) over time by month and (2) overall, by migraine intensity (total; moderate or severe)
Summary	Summary statistics for values and changes from OP over time for the migraine analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective	**MSQ domain scores and changes from baseline**
Outcomes Research Endpoint	Values and changes from baseline in the MSQ score over time for each dimension
Summary	Summary statistics for values and changes from baseline over time for each dimension for the safety analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective	**PoM**
Outcomes Research Endpoint	Number and percentage of subjects in each of 5 preference categories (much better to much worse) of study medication relative to previous migraine medications
Summary	Frequency for the safety analysis set with PoM data
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective	**SM**
Outcomes Research Endpoint	Number and percentage of subjects in each of 7 satisfaction categories (completely satisfied to completely dissatisfied) of study medication
Summary	Frequency for the safety analysis set with SM data
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective	**MIDAS scores and changes from baseline**
Outcomes Research Endpoint	Values and changes from baseline in the MIDAS score over time for each dimension
Summary	Summary statistics for values and changes from baseline over time for each dimension for the safety analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy
Objective	**CGI-c**
Outcomes Research Endpoint	Number and percentage of subjects in each of 7 improvement categories (very much improved to very much worse) relative to investigator's past experience with other patients with the same diagnosis over time
Summary	Frequency over time for the safety analysis set with CGI-c data
Intercurrent Events	Study drug discontinuation: treatment policy strategy

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

The following analysis sets are evaluated and used for presentation and analysis of the data:

- Enrolled: Subjects who sign an informed consent form and are assigned a subject identification number, i.e., non-missing informed consent date. This analysis set is used mainly to assess study population and in by-subject listings.
- LTT participated: Subjects in the enrolled analysis set who participated in the LTT phase, i.e., non-missing IWRS baseline visit date. This analysis set is used mainly to assess study population.
- Safety: Subjects in the enrolled analysis set who take study drug, i.e., non-missing study drug start date/time. This analysis set is used to assess study population, exposure, and on-treatment safety, migraine days per month, and outcomes research.
    - Migraine: Subjects in the safety analysis set with ≥ 14 days of data (not necessarily consecutive) in both the OP analysis period and ≥ 1 month in the LTT analysis period. This analysis set is used to assess migraine days per month.
    - Follow-up: Subjects in the safety analysis set whose last contact date is in the follow-up safety analysis period. This analysis set is used to assess follow-up safety.
- Full: Subjects in the LTT participated or safety analysis set.
- Coronavirus Disease 2019 (COVID-19) impacted: Subjects in the enrolled analysis set who are impacted by COVID-19 (see Section 9.1.2).

See Section 7.1 for derived dates and Section 7.2 for analysis periods.

4.2 Treatment Groups

The single treatment group is zavegepant 10 mg.

4.3 Subgroups

The following safety subgroups are of interest for the safety analysis set:

- Intrinsic factors
    - Age at informed consent (years): < 40, ≥ 40, < 65, ≥ 65
    - Sex: female, male
    - Race: White, Black or African American, other including Asian, Asian
    - Ethnicity: Hispanic or Latino, not Hispanic or Latino
    - Cardiovascular risk factors contraindicating triptans: yes, no (refer to the Zavegepant Core SAP)
    - Baseline body mass index (BMI; kg/m^2): < 25, ≥ 25 to < 30, ≥ 30

- Extrinsic factors
  - Average zavegepant exposure (sprays per month): < 6, ≥ 6 (see Section 6.2.5.1).
  - Cumulative zavegepant exposure (sprays): < 20, ≥ 20 to < 40, ≥ 40 to < 60, ≥ 60 to < 80, ≥ 80 (see Section 6.2.5.1)
  - Time on zavegepant (weeks): < 12, ≥ 12 to < 24, ≥ 24 to < 36, ≥ 36 to 48, ≥ 48 (see Section 6.2.5.1)
  - Concomitant prophylactic migraine medication use: yes, no (see Section 6.2.5.4)
  - Current or concomitant approved biologics use (yes, no; see Section 6.2.5.4)
  - Total treated migraine days per month in the overall LTT (< 2, ≥ 2; see Section 6.4.6.2).

Subgroup tables present results by subgroup level and overall for subjects with non-missing subgroup level data. Subgroup levels may be redefined or combined based on the availability of data.

5 SAMPLE SIZE, POWER, AND TYPE 1 ERROR

With a sample size of 600 treated subjects and no events observed, the upper bound of a one-sided 95% confidence interval for zero observations is 0.005. Hence this sample size is large enough to rule out AEs that occur at rates greater than 5 cases per 1,000 subjects.

6 STATISTICAL ANALYSES

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

6.1 General

6.1.1 Programmed Output

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

Tables present results by the single treatment group (i.e., zavegepant 10 mg).

Refer to the Zavegepant Core SAP for additional details about programmed output.

6.1.1.1 Time-to-event Tables and Plots

Time-to-event endpoints are summarized with Kaplan-Meier tables and plots. Refer to the Zavegepant Core SAP for additional details.

6.1.1.2 Listings

Unless specified otherwise, by-subject listings are sorted by treatment status (treated, not treated), site-subject ID, and additional variables such as time points, as applicable.

All listings except listings of batch numbers identify subjects who are impacted by COVID-19 (see Section 9.1.2).

Listings of significant protocol deviations, non-study medications, safety parameters, outcomes research parameters, and COVID-19 visit impact display both study day and treatment day (see Section 7.3). Other listings display study day only, if applicable.

Listings of significant protocol deviations, safety parameters, outcomes research parameters, and COVID-19 visit impact include the following: abbreviated name of the analysis period in which the measurement was slotted (i.e., PRELTT, LTT, FU; this does not apply to outcomes research parameters); analysis visit in which the measurement was slotted (this does not apply to AEs); measurement date/time; study day and treatment day derived using the measurement date.

Select listings of measurements over time display COVID-19 visit impact code for visits that are impacted by COVID-19 (see Section 9.1.5.2).

Refer to the Zavegepant Core SAP for additional details about listings.

6.1.2 Statistical Methods

Refer to the Zavegepant Core SAP for descriptive statistics in summary tables, counting rules in frequency tables, and rounding rules.

6.1.3 Missing Data

All analyses are based on observed data without using imputation.

6.2 Study Population

6.2.1 Analysis Sets

The number of subjects in each analysis set described in Section 4.1 is tabulated.

A by-subject listing of analysis sets is provided for the enrolled analysis set. Refer to the Zavegepant Core SAP for listing contents.

6.2.2 Enrollment

Enrollment by (1) country and site and (2) age group are tabulated for the enrolled analysis set. The enrollment by country and site table also displays results for the full and safety analysis sets. Refer to the Zavegepant Core SAP for additional details.

Accrual by month and year of LTT start is tabulated as the number and percentage of subjects in each time category (i.e., month and year of LTT start date) for the full analysis set. See Section 7.1 for derived dates.

6.2.3 Subject Disposition

Subject disposition is based on the Study Exit Status case report form (CRF), unless noted otherwise. Note that the Study Exit Status CRF links non-completion due to AE to the AE CRF using numeric variables.

Refer to the Zavegepant Core SAP for displaying reasons for not completing a milestone.

A by-subject listing of subject disposition is provided for the enrolled analysis set based on the Study Exit Status CRF, and includes the following: study completion status (yes, no, ongoing); reason for not completing the study, including specify text for "other" and AE preferred terms (PTs); LTT start date; LTT end date; study drug start date; study drug end date; last contact date; previous study treatment group(s); and previous study subject identifier. The listing also identifies subjects who terminated the study prematurely due to COVID-19 (see Section 9.1.4). See Section 7.1 for derived dates.

A by-subject listing of eligibility with inclusion and exclusion criteria is provided for all subjects in the enrolled analysis set, not just those who have non-missing criteria. This is based on the Inclusion/Exclusion Criteria CRF.

6.2.3.1 Subject Disposition from Enrollment to LTT Participation

Subject disposition from enrollment to LTT participation is tabulated for the enrolled analysis set as the number and percentage of subjects in the following categories:

- LTT participated (identified as those with non-missing IWRS baseline visit date).
- Not LTT participated (identified as those with missing IWRS baseline visit date)
  - Did not enter the OP (identified as those with missing OP start date)
    - Reasons for early discontinuation (i.e., not completing the DBT Phase), including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure from the Inclusion/Exclusion Criteria CRF are also included as subcategories.
  - Entered the OP (identified as those with non-missing OP start date)
    - Reasons for early discontinuation, including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure from the Inclusion/Exclusion Criteria CRF are also included as subcategories.
- Not LTT participated and terminated the study prematurely due to COVID-19 (see Section 9.1.4). This has the same subcategories as "Not LTT participated".

6.2.3.2 Subject Disposition from LTT Participation to Treatment

Subject disposition from LTT participation to treatment is tabulated for the LTT participated analysis set as the number and percentage of subjects in the following categories:

- Treated with study drug (identified as those with non-missing study drug start date)

- Not treated with study drug (identified as those with missing study drug start date)
    - Reasons for early discontinuation (i.e., not completing the DBT Phase), including not reported
- Not treated with study drug and terminated the study prematurely due to COVID-19 (see Section 9.1.4)
    - Reasons for premature termination, including not reported.

6.2.3.3 Subject Disposition from Treatment through Follow-up

Subject disposition from treatment through follow-up is tabulated for the safety analysis set as the number and percentage of subjects in the following categories:

- Ongoing in the study (identified as those with missing response to the question "Did the subject complete the study (including the follow-up visit)?"). This category only exists before the final database lock. After the final database lock, subjects with missing response are categorized as "Did not complete the study".
- Completed the study (identified as those with "yes" response to the question "Did the subject complete the study (including the follow-up visit)?")
- Did not complete the study (identified as those with "no" response to the question "Did the subject complete the study (including the follow-up visit)?")
    - Reasons for early discontinuation, including not reported
- Terminated the study prematurely due to COVID-19 (see Section 9.1.4)
    - Reasons for premature termination, including not reported.

6.2.3.4 Overall Premature Study Termination due to COVID-19

Overall premature study termination due to COVID-19 is tabulated for the enrolled analysis set as the number and percentage of subjects in categories defined by reasons for premature termination, including not reported.

6.2.3.5 Treatment in Previous Studies

Treatment in previous studies BHV3500-201 and BHV3500-301 is tabulated for the following analysis sets: enrolled; LTT participated; safety. The number and percentage of subjects who took study drug in each previous study (total; 201; 301) and as-treated treatment group (zavegepant, placebo) are presented for each analysis set together in a single table. Note that subjects may take study drug in multiple studies and be in both treatment groups.

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

Relevant protocol deviations are tabulated as the number and percentage of subjects with deviations by deviation type (eligibility, subject management), category, and subcategory in the order specified in Section 9.2 for the full analysis set. Results for all relevant protocol deviation categories and subcategories are displayed, even those with 0 counts, unless specified otherwise.

A by-subject listing of relevant protocol deviations is provided for the enrolled analysis set. This includes deviation type, category, and subcategory, which are used as additional sorting variables.

6.2.4.2 Significant Protocol Deviations

A by-subject listing of significant protocol deviations is provided for the enrolled analysis set. This includes date of deviation, category, (e.g., Eligibility Criteria), subcategory (e.g., Violation of Exclusion Criteria), and description, which are used as additional sorting variables.

A Microsoft Excel file of protocol deviations is extracted from the clinical trial management system (CTMS) by Biohaven Clinical Operations. This file serves as the raw data source of protocol deviations, and classifies deviation severity as major, minor, or downgraded from protocol deviation. Significant protocol deviations are defined as those with major severity.

6.2.5 Baseline Characteristics

Baseline characteristics include (1) demographics and other relevant baseline characteristics, (2) baseline disease characteristics (i.e., migraine history, cardiac and other risk factors, prior triptan response, and current triptan response), (3) medical history, and (4) prior non-study medications. Baseline characteristics are tabulated for each of the following analysis set sets:

- Safety analysis set
  - Baseline characteristics (1) though (4)
  - Demographics and other relevant baseline characteristics, and migraine history by subgroup level and overall by all subgroups of interest defined in Section 4.3
- Enrolled analysis set but not in the safety analysis set: Demographics and other relevant baseline characteristics, and migraine history
- Migraine analysis set: Demographics and other relevant baseline characteristics, and migraine history.

Baseline for a parameter (e.g., weight) is defined according to analysis set as follows:

- Enrolled analysis set but not in the LTT participated analysis set: Last non-missing value
- LTT participated analysis set but not in the safety analysis set: Last non-missing value on or before the IWRS baseline visit date

- Safety, migraine, and outcomes research analysis sets: Last non-missing value in the pre-treatment analysis period; see Sections 7.1 and 7.2).

"Last" is determined by the measurement date/time. Other criteria such as last entry date/time may be applied to break ties on the same measurement date, as available from CRF data. See Sections 6.4.2.3, 6.4.3.1, 6.4.4.1, and 6.5 for handling of ties on the same measurement date or time. Note that the baseline value of a parameter is independent of the baseline analysis visit defined in Table 3; the latter is used only in by-subject listings that display visit, and in COVID-19 analyses by analysis visit (see Sections 6.6.2 and 6.6.3).

By-subject listings are provided for the enrolled analysis set for the following: demographics; medical history; migraine history; cardiac and other risk factors for subjects with any risk factor present; prior triptan response; and current triptan response. Refer to the Zavegepant Core SAP for additional details.

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Zavegepant Core SAP for the table of demographics and other relevant baseline characteristics. Previous study participation (e.g., any study, BHV3500-201, BHV3500-301) is also displayed.

6.2.5.2 Baseline Disease Characteristics

Refer to the Zavegepant Core SAP for tables of migraine history, cardiac and other risk factors, prior triptan response, and current triptan response.

6.2.5.3 Medical History

Medical history is tabulated by system organ class (SOC) and PT, and displayed in descending order of overall frequency within SOC and PT.

6.2.5.4 Prior Medications

The following non-study medications are tabulated by therapeutic class and preferred name for the safety analysis set:

- Prior medications: all; migraine standard of care; prophylactic migraine
- Current medications: all; migraine standard of care; prophylactic migraine
- Pre-LTT medications: all; migraine standard of care; prophylactic migraine
- OP medications: all; migraine standard of care; prophylactic migraine.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See Section 6.2.6.3.

Refer to the Zavegepant Core SAP for the definitions of prior and concurrent medications.

Pre-LTT medications are defined as those taken on or after informed consent and before LTT start, i.e., those meeting any of the following criteria:

- Informed consent date ≤ imputed start date or imputed stop date ≤ LTT start date – 1
- Informed consent date ≤ imputed start date or imputed stop date, and LTT start date is missing
- Imputed start date ≤ informed consent date < LTT start date – 1 ≤ imputed stop date
- Imputed start date ≤ informed consent date ≤ imputed stop date, and LTT start date is missing.

OP medications are defined as those taken during the OP, i.e., those with (1) OP start date ≤ imputed start date or imputed stop date ≤ OP end date, or (2) imputed start date ≤ OP start date ≤ OP end date ≤ imputed stop date.

6.2.6 Exposure

Study drug is zavegepant 10 mg IN spray.

Subjects provide study drug taken status (yes, no), number of sprays administered, and nostril location of each spray (left, right) in the eDiary every day after they are determined to be eligible to take study drug. Sites may enter this information on the eDiary medication reconciliation form for missed doses. Days on which a subject took study drug are determined by records with non-missing study drug date/time (see Section 7.1). If there are no study drug data in the eDiary on a given day, then it is assumed that the subject did not take study drug that day.

Study drug accountability is provided by the site on the Drug Accountability CRF. There are 4 single-use devices in each kit. Sites provide the number of unused devices in each kit dispensed and returned.

6.2.6.1 Study Therapy

A by-subject listing presents eDiary study drug exposure and study drug accountability for the full analysis set as follows:

- Study day and treatment day derived respectively from eDiary study drug dates and drug accountability kit dispensed dates
- eDiary: study drug date/time, source (evening report or medication reconciliation form), number of sprays administered, nostril location of each spray. Only eDiary records with non-missing study drug date/time and number of sprays > 0 are displayed.
- Drug accountability: kit dispensed and kit returned status (yes, no), kit dispensed date, kit returned date, kit ID, all investigational product (IP) used status (yes, no), number of IP devices not used. Invalid kit IDs are identified.

The listing also displays COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

Another by-subject listing presents eDiary study drug exposure (i.e., total number of sprays administered) by nostril location (left, right, total) by month during the LTT for the safety analysis set. This also displays cumulative zavegepant exposure from both sources (i.e., eDiary and drug accountability), and identifies subjects with ≥ 10 cumulative absolute spray difference between the 2 sources.

An administrative listing of IP batch numbers is provided for the safety analysis set. Refer to the Zavegepant Core SAP for listing contents.

eDiary Zavegepant and LTT Exposure

eDiary zavegepant and LTT exposure is tabulated as continuous or categorical variables for the safety analysis set, and includes the following parameters:

- Time in the OP (weeks), derived as (OP end date – OP start date + 1)/7
- Time from LTT start to last contact (weeks), derived as (last contact date – LTT start date + 1)/7
- Time in the LTT period (weeks), derived as (LTT end date – LTT start date + 1)/7
- Time in the LTT period (weeks) categories: ≥ 11, ≥ 23, ≥ 51. These correspond to using a 1-week lower bound on 3, 6, and 12 months, respectively.
- Time on zavegepant (weeks), derived as (study drug end date – study drug start date + 1)/7
- Time on zavegepant (weeks) categories: <12, ≥ 12 to < 24, ≥ 24 to < 36, ≥ 36 to < 48, ≥ 48. These align with subgroups specified in Section 4.3.
- Cumulative zavegepant exposure (sprays), derived by summing number of sprays across records with complete study drug dates
- Cumulative zavegepant exposure (sprays) categories: < 20, ≥ 20 to < 40, ≥ 40 to < 60, ≥ 60 to < 80, ≥ 80. These align with subgroups specified in Section 4.3.
- Average zavegepant exposure (sprays per month), derived as (1) cumulative zavegepant exposure (sprays) if time in the LTT period < 2 weeks, or (2) 4 × cumulative zavegepant exposure/time in the LTT period if time in the LTT period ≥ 2 weeks.
- Average zavegepant exposure (sprays per month) categories: < 6, ≥ 6. These align with subgroups specified in Section 4.3.
- Number and percentage of subjects who administered > 1 spray on any 1 day
- Number and percentage of subjects who administered > 8 sprays per month in any month
- Exposure categories, defined as the number and percentage of subjects who administered
    - ≥ 1 spray per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months
    - ≥ 2 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months
    - ≥ 3 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months

  - ≥ 4 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months
  - ≥ 5 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months
  - ≥ 6 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months
  - ≥ 7 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months
  - ≥ 8 sprays per month for 1, 2, 3, 4, 5, ≥ 12, ≥ 6, ≥ 3 and ≥ 1 months.
- Total zavegepant exposure (sprays) summed across all subjects, derived by summing cumulative exposure across all subjects
- Total zavegepant exposure (patient-years), derived by summing (study drug end date – study drug start date + 1)/365.25 across all subjects.

See Section 7.1 for derived dates.

eDiary zavegepant and LTT exposure is also tabulated by subgroup level and overall for the safety analysis set for all subgroups of interest described in Section 4.3.

Months are 4-week (28-day) intervals in the LTT analysis period defined as follows:

- Month 1 (≤ 4 weeks; study days 1 to 28)
- Month 2 (> 4 to ≤ 8 weeks; study days 29 to 56)
- Month 3 (> 8 to ≤ 12 weeks; study days 57 to 85)
- Month 4 (> 12 to ≤ 16 weeks; study days 85 to 112)
- Month 5 (> 16 to ≤ 20 weeks; study days 113 to 140)
- Month 6 (> 20 to ≤ 24 weeks; study days 141 to 168)
- Month 7 (> 24 to ≤ 28 weeks; study days 169 to 196)
- Month 8 (> 28 to ≤ 32 weeks; study days 197 to 224)
- Month 9 (> 32 to ≤ 36 weeks; study days 225 to 252)
- Month 10 (> 36 to ≤ 40 weeks; study days 253 to 280)
- Month 11 (> 40 to ≤ 44 weeks; study days 281 to 308)
- Month 12 (> 44 to ≤ 48 weeks; study days 309 to 336)
- Month 13 (> 48 to ≤ 52 weeks; study days 337 to 364)
- Month 14 (> 52 to ≤ 56 weeks; study days 365 to 392).

See Section 7.3 for the definition of study days.

Exposure categories assess the number of months in which a subject exceeded select spray counts in the LTT analysis period (see Section 7.2), where the number of months are not necessarily consecutive. For example, suppose a subject administers 4 sprays in Month 1, 3 sprays in Month 2, 5 sprays in Month 3, 6 sprays in Month 4, and 0 sprays in Month 5. Thus, this

subject is considered to have administered ≥ 2 sprays per month for 4 months (i.e., Months 1 through 4), ≥ 4 sprays per month for 3 months (i.e., Months 1, 3 and 4), and ≥ 6 sprays per month for 1 month (i.e., Month 4).

eDiary Zavegepant Sprays per Month Over Time

eDiary zavegepant sprays per month over time are tabulated as a continuous variable at each month in the LTT analysis period for the safety analysis set. This analysis is based on absolute spray counts per month. Using the example above for exposure categories, the subject has 4, 3, 5, 6, and 0 sprays per month in Months 1 through 5, respectively, and 5 months in the LTT period as determined by calculating the ceiling([LTT end date – LTT start date + 1]/28).

This is also tabulated for the safety analysis set with ≥ 51 weeks in the LTT period.

eDiary Time on Zavegepant and in LTT

Kaplan-Meier mortality tables summarize time on zavegepant and time in the LTT period in 4-week intervals (i.e., ≤ 4, > 4 to ≤ 8, …, > 52) for the safety analysis set. A Kaplan-Meier mortality plot displays the percentage of subjects in the LTT period (y-axis) versus weeks (x-axis). Subjects with non-missing response to the question "Did the subject complete the study?" on the Study Exit Status CRF are considered to have discontinued both zavegepant and the LTT period; otherwise, in an interim analysis, subjects are censored at the study drug end date or the LTT end date, respectively.

Study Drug Accountability Exposure

Study drug accountability exposure is tabulated as a continuous variable for the safety analysis set, and includes the following parameters:

- Time from first kit dispensed to last kit returned (weeks), derived as (latest kit return date – earliest kit dispense date + 1)/7. Subjects who were dispensed at least 1 kit but never returned any kit are credited with 1 day.

- Cumulative zavegepant exposure (sprays) based on kits dispensed and returned, derived as summing (4 - number of unused devices remaining in each kit) across records with non-missing kit dispense and return dates.

- Average zavegepant exposure (sprays per month) based on kits dispensed and returned, derived as 4 × cumulative zavegepant exposure based on kits dispensed and returned/time from first kit dispensed to last kit returned.

eDiary Versus Drug Accountability Cumulative Study Drug Exposure

eDiary versus drug accountability cumulative study drug exposure is tabulated as the number and percentage of subjects in the safety analysis set with 0, ≥ 10, ≥ 20, ≥ 30, ≥ 40, ≥ 50 absolute spray difference, derived as the absolute value of (eDiary study drug cumulative exposure [sprays] – study drug accountability cumulative exposure [sprays]).

6.2.6.2 Measurements of Treatment Compliance

eDiary Usage Compliance

eDiary usage compliance is tabulated for the safety analysis set, for each source (subject; subject or site). Data days are records with complete eDiary finding dates. Usage compliance is derived for the following parameters:

- Last 28 days before LTT start: 100 × (total number of data days from the [LTT start date – 28 days] to the [LTT start date – 1 day])/28
- LTT start to LTT end: 100 × (total number of data days from the LTT start date to the LTT end date)/(LTT end date – LTT start date + 1).

eDiary usage compliance is tabulated as a continuous variable and as the number and percentage of subjects in the following categories: ≥ 90% compliance; ≥ 80% compliance. Subject sources are the evening report, PoM, and SM. The site source is the medication reconciliation form.

Study Drug Accountability Compliance

Study drug accountability compliance is tabulated for the full analysis set as the number and percentage of subjects in the following categories:

- ≥ 1 kit dispensed
- Did not return ≥ 1 kit dispensed and discontinued the study
- Did not return any kit dispensed and discontinued the study

Kit dispensed and kit returned are identified from "yes" responses to the questions "was this kit dispensed" and "was this kit returned", respectively. Subjects who have non-missing study drug last date are considered to have discontinued the study.

6.2.6.3 Concomitant Medications

The following concomitant non-study medications are tabulated by therapeutic class and preferred name for the safety analysis set: all; migraine standard of care; prophylactic migraine.

In addition, current or concomitant calcitonin gene-related peptide (CGRP) receptor antagonist biologics are tabulated analogously to support safety subgroup analyses and align with subgroups specified in Section 4.3. Refer to the Zavegepant Core SAP for preferred names.

The following non-study medications taken on or after LTT start are tabulated by therapeutic class and preferred name for the safety analysis set: all; migraine standard of care; prophylactic migraine. These are medications with LTT start date ≤ imputed start date or imputed stop date.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. Imputed medication start and stop dates are used to assign non-study medication type (previous, current, concomitant, or follow-up) to all non-study medications except rescue

medications. Refer to the Zavegepant Core SAP for definitions of non-study medication types, non-study medication counting rules in frequency tables, and non-study medication start and stop date imputation.

A by-subject listing of non-study medications is provided by therapeutic class and preferred name for the enrolled analysis set. Acute migraine and prophylactic migraine medications are identified, as well as medication type. The listing also displays treatment days derived from the imputed start date, and COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2). Refer to the Zavegepant Core SAP for additional listing contents.

The following conventions apply to non-study medications:

- Non-study medications are identified from those reported on the Concomitant Medication CRF, which links medical history and AE terms respectively to the Medical History and AE CRFs using numeric variables.
- Migraine standard of care medications are defined as either acute migraine or prophylactic migraine medications from the indication panel of the CRF.

6.3 Efficacy

Not applicable.

6.4 Safety

Safety analyses are based on the safety analysis set, unless otherwise noted. Safety parameters include the following: deaths; AEs; laboratory tests; vital signs; physical measurements; electrocardiograms (ECGs); and S-STS.

Refer to the Zavegepant Core SAP for slotting safety parameters into analysis periods.

Select safety parameters are tabulated descriptively as continuous variables at baseline and each scheduled visit over time during the on-treatment and follow-up safety analysis periods. Measurements are slotted into analysis periods and analysis visits using the following steps:

1) Measurements are slotted into the pre-LTT, LTT and follow-up analysis periods.
2) Measurements are slotted into analysis visits in the analysis periods listed in the previous step.
3) Measurements are slotted into safety analysis periods (pre-treatment, on-treatment and follow-up).

For tables of safety parameters excluding laboratory tests summarized over time, if a subject has multiple values in an analysis visit window in a safety analysis period, then the non-missing value measured closest to the target date for the visit is used. In the case of a tie, the last non-missing value measured is used. In these tables, results are also summarized at the EOT visit using the last non-missing value measured in the on-treatment safety analysis period. See Sections 6.4.3.1 and 6.4.4.1 for further handling of ties on the same measurement date or time.

Note that a different algorithm is used for selecting a laboratory test value in an analysis visit window (see Section 6.4.2.3).

See Sections 6.2.4, 7.2, and 7.3 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

By-subject listings of safety parameters are described in subsections. In addition, a by-subject listing of procedures is provided for the enrolled analysis set. Listings identify events or findings during the on-treatment safety analysis period, and display COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

The terms "on-treatment" and "follow-up" apply to the on-treatment and follow-up safety analysis periods, respectively.

6.4.1 Adverse Events

Refer to the Zavegepant Core SAP for AE start date imputation, AE counting rules, definition of treatment-emergent adverse events (TEAEs), definition of AEs related to study drug, definition of AEs of special interest, definition of exposure-adjusted multiple occurrences of unique AEs, and AE listing contents.

Tables present the number and percentage of subjects experiencing AEs by SOC and PT, unless specified otherwise.

The following by-subject AE listings are provided for the enrolled analysis set, unless specified otherwise: AEs (displays COVID-19 visit impact code for visits impacted by COVID-19; see Section 9.1.5.2); SAEs; AEs leading to study drug discontinuation for the safety analysis set; and AEs of special interest (i.e., potential drug abuse, medication-overuse headache, hepatic-related, cardiovascular, suicidality, and local irritation). TEAEs are identified.

6.4.1.1 Deaths

Deaths are identified from any the following sources:

- AE CRF: PT or reported term containing "death", outcome of fatal, "yes" response to the question "Did the AE result in death?", or non-missing death date.
- Study Exit Status CRF: study non-completion reason of death.

Deaths are tabulated by analysis period for the enrolled analysis set.

A by-subject listing of deaths is provided for the enrolled analysis set, and displays all CRF sources of death, safety analysis period, death date (see Section 7.1), study day derived from the death date, treatment day derived from the death date, and the following AE parameters: non-imputed start date; end date; SOC; PT; verbatim term; outcome; and response to the question "Did the AE result in death?". Refer to the Zavegepant Core SAP for additional details.

6.4.1.2 AE Overview

An AE overview without SOC and PT presents the number and percentage of subjects with any the following AEs: any AE; mild AE; moderate AE; severe AE; moderate or severe AE; AE related to study drug; AE leading to study drug discontinuation; SAE; SAE related to study drug; SAE leading to study drug discontinuation; potential drug abuse AE; medication-overuse headache AE; hepatic-related AE; local irritation AE; cardiovascular AE; and suicidality AE.

An AE overview is produced for each the following analysis periods and analysis sets:

- Pre-treatment AEs for the enrolled analysis set
- Pre-treatment AEs for the safety analysis set
- On-treatment AEs for the safety analysis set
- On-treatment AEs for the safety analysis set by subgroup level and overall for all subgroups of interest specified in Section 4.3
- TEAEs for the safety analysis set
- Follow-up AEs for the follow-up analysis set.

6.4.1.3 Pre-treatment AEs

Pre-treatment AEs are tabulated by SOC and PT for the enrolled analysis set for the following endpoints:

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

Pre-treatment AEs are tabulated by SOC and PT for the safety analysis set for the following endpoints:

- AEs by intensity
- SAEs.

6.4.1.4 On-treatment AEs

On-treatment AEs are tabulated for the safety analysis set by SOC and PT for the following endpoints:

- AEs by intensity *
- AEs occurring with ≥ 5% frequency by intensity (primary safety endpoint). The 5% cut applies only to total intensity.
- AEs occurring with ≥ 10% frequency
- TEAEs by intensity

- TEAEs occurring with ≥ 2% frequency after rounding. Percentages are displayed rounded to integers, and AEs are displayed in alphabetical order by SOC and PT.
- AEs related to study drug by intensity *
- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs (primary safety endpoint)
- AEs leading to study drug discontinuation (primary safety endpoint)
- AEs of special interest
    - Potential drug abuse AEs, displayed in alphabetical order by intensity and PT without SOC (exploratory safety endpoint)
    - Medication-overuse headache AEs (exploratory safety endpoint)
    - Hepatic-related AEs by intensity (exploratory safety endpoint)
    - Local irritation AEs by intensity (exploratory safety endpoint)
    - Cardiovascular AEs
    - Suicidality AEs
- Exposure-adjusted multiple occurrences of unique AEs
- Exposure-adjusted multiple occurrences of unique SAEs
- Exposure-adjusted multiple occurrences of unique SAEs related to study drug
- Exposure-adjusted multiple occurrences of unique non-SAEs occurring with ≥ 5% frequency.

Endpoints marked with "*" are also tabulated by subgroup level and overall for all subgroups of interest specified in Section 4.3.

Calculations for on-treatment exposure-adjusted multiple occurrences of unique AEs set the reference start date to the study drug start date, reference end date to the study drug end date, and reference last date to the study drug last date + 7 days.

6.4.1.5 Follow-up AEs

Follow-up AEs are tabulated by SOC and PT for the follow-up analysis set for the following endpoints:

- AEs by intensity
- SAEs.

6.4.1.6 AEs in All Safety Analysis Periods Combined

AEs in all safety analysis periods combined (i.e., pre-treatment, on-treatment, and follow-up) are tabulated by SOC and PT for the safety analysis set for the following endpoints:

- AEs leading to study drug discontinuation
- Hepatic-related AEs leading to study drug discontinuation
- Local irritation AEs leading to study drug discontinuation.

6.4.2 Laboratory Tests

Laboratory tests are analyzed using results from the external central laboratory CCI [redacted] which identifies expired kits, and from local laboratory tests reported on CRFs. The central laboratory reports both laboratory collection date and time, whereas CRFs capture only laboratory collection date.

Laboratory tests of clinical interest are collected at the following visits:

- Hematology: Screening; Pre-Baseline; Weeks 4, 24, and 52; and early termination.
- Serum chemistry (including LFTs and lipids): Screening; Pre-Baseline; Weeks 4, 24, and 52; and early termination. Exceptions are for the following:
  - LFTs (ALT, AST, ALP, TBL, direct bilirubin, indirect bilirubin): Screening; Pre-Baseline; all visits during the treatment period; early termination; and Follow-up Week 2.
  - Lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides): Pre-Baseline; Weeks 24 and 52; and early termination.
- Urinalysis: Pre-Baseline; Week 52; and early termination.

Clinically significant laboratory abnormalities are identified as grade 3 to 4 laboratory test results. Refer to the Zavegepant Core SAP for laboratory tests of clinical interest for analyses, including identification of those with toxicity grades.

The following by-subject laboratory test listings are provided for the enrolled analysis set:

- Select laboratory test groups: hematology (both SI and US units)*; serum chemistry, including LFTs (both SI and US units)*; urinalysis (US units only)*; pregnancy (US units only)*; endocrinology, serology, drug screen, and miscellaneous laboratory tests (US units only). The pregnancy listing identifies positive pregnancy tests, which are defined as serum or urine pregnancy tests with either (a) “positive” character value, or (b) numeric value ≥ 25 U/L.

- LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) for both US and SI units*. The listing displays all LFT results over time for subjects with select LFT elevations (ALT or AST > 3x ULN; ALP or TBL > 2x ULN) at any time point.

- Creatine kinase (CK) elevation questionnaire.

Listings display toxicity grades and identify expired kits from the central laboratory, if applicable, and those marked with "*" display COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2). Refer to the Zavegepant Core SAP for listing contents.

6.4.2.1 Laboratory Test Abnormalities

On-treatment laboratory test abnormalities are tabulated as the number and percentage of subjects in the safety analysis set in the following frequency tables:

- Worst (highest) on-treatment laboratory test abnormality for each graded laboratory test *. Grade 3 to 4 results support the primary objective.
- Laboratory test toxicity grade shift from baseline to the worst on-treatment toxicity grade for each graded laboratory test.
- Laboratory test low/normal/high shifts from baseline to any abnormal on-treatment value for each laboratory test with normal ranges.

Refer to the Zavegepant Core SAP for toxicity grade categories and additional details.

Endpoints marked with "*" are also tabulated (1) on treatment by subgroup level and overall for all subgroups of interest specified in Section 4.3 for the safety analysis set, and (2) during follow-up for the follow-up analysis set.

6.4.2.2 Liver Function Test Elevations

Refer to the Zavegepant Core SAP for additional details.

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

LFT elevations are based on fold changes above ULN. The number and percentage of subjects with LFT elevations are tabulated separately for the following each analysis periods and analysis sets:

- Pre-treatment for the enrolled analysis set
- Pre-treatment for the safety analysis set
- On-treatment for the safety analysis set
- Follow-up for the follow-up analysis set.

LFT ULN Shifts from Baseline to Worst Elevation

LFT ULN shifts from baseline to the worst (highest) on-treatment LFT elevation are tabulated as the number and percentage of subjects in the safety analysis set in pre-specified elevation categories.

Exposure-adjusted Cumulative LFT Elevations

Exposure-adjusted cumulative on-treatment LFT elevations are tabulated. Calculations set the reference start date to the study drug start date, reference end date to the study drug end date, and reference last date to the study drug last date + 7 days.

Time to LFT Elevations

The number and percentage of subjects in the safety analysis set with time to first on-treatment LFT elevations (ALT > 3x ULN; AST > 3x ULN; ALT or AST > 3x ULN) are presented for subjects with on-treatment LFT elevations in the following categories: ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, …, > 48 to ≤ 52, > 52 weeks. Time to elevation is calculated as (LFT collection date – study drug start date + 1)/7.

LFT Plots

An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot displays the maximum TBL ratio of value to ULN on the y-axis versus the maximum ALT ratio of value to ULN on the x-axis by treatment group, where both maxima are on treatment but not necessarily concurrent.

By-subject longitudinal LFT plot displays ratios of values to ULN for AST, ALT, ALP, and TBL on the y-axis versus study week of the laboratory test result on the x-axis for subjects in the safety analysis set with any of the following LFT elevations in any safety analysis period: ALT > 3x ULN; AST > 3x ULN; TBL > 2x ULN; ALP > 2x ULN. Study weeks are defined as study day/7, where study day is derived from the laboratory test collection date (see Section 7.3). Each figure also displays treated migraine days using symbols along the x-axis (see Section 6.4.6), and denotes additional study milestones (e.g., start of the on-treatment safety analysis period, and start of the follow-up safety analysis period) using vertical lines with their corresponding descriptions in footnotes.

6.4.2.3 Laboratory Test Changes from Baseline

Values and changes from baseline in hematology and serum chemistry laboratory tests are tabulated descriptively as continuous variables at baseline and each scheduled visit in the on-treatment and follow-up safety analysis periods.

If a subject has multiple values in an analysis visit window in a safety analysis period, then a single value is selected using the following hierarchy as available:

- Non-missing viable value collected closest to the target date for the visit. In the case of a tie, the last non-missing viable value collected is used. If there are multiple viable values on the same date, then the following hierarchy is used as available:
    - Last central laboratory test value collected timewise with the last accession identifier.
    - Last local laboratory test value entered.

Viable laboratory test values are defined as those from (1) kits from the central laboratory that are not expired (see Section 6.4.2), or (2) local laboratory tests reported on CRFs.

- Non-missing value from an expired kit from the central laboratory collected closest to the target date for the visit. In the case of a tie, the last non-missing value collected with the last accession identifier is used.

Results are also summarized at the EOT visit with a single value in the on-treatment safety analysis period using the following hierarchy as available:

- Last non-missing viable value collected. See above for handling multiple viable values on the same date.
- Last non-missing value collected with the last accession identifier from an expired kit from the central laboratory.

6.4.3 Vital Signs and Physical Measurements

All parameters are reported with measurement date only (no time).

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate. These parameters are measured at Screening, Pre-Baseline, every visit during the treatment period, early termination, and Follow-up Week 2.

Physical measurements include height (measured at Screening only), weight, and BMI.

A by-subject listing of vital signs and physical measurements is provided for the enrolled analysis set, and displays COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

6.4.3.1 Vital Sign and Physical Measurement Changes from Baseline

Values and changes from baseline in vital signs and physical measurements are tabulated descriptively as continuous variables at baseline and each scheduled visit in the on-treatment and follow-up safety analysis periods for the safety analysis set.

If there are multiple values on the same measurement date, then the last value entered is used.

6.4.3.2 Vital Sign and Physical Measurement Abnormalities

On-treatment vital sign and physical measurement abnormalities are tabulated as the number and percentage of subjects in the safety analysis set in categories specified in the Zavegepant Core SAP.

Follow-up vital sign and physical measurement abnormalities are tabulated analogously for the follow-up analysis set.

6.4.4 Electrocardiogram

ECG parameters include RR, QRS, PR, QT, QTcB, QTcF, and ventricular heart rate. ECGs are measured with both acquisition date and time by the external source [CCI] at the following visits: Screening; Weeks 4, 24, and 52; early termination; Follow-up Week 2.

A by-subject listing of ECG results is provided for the enrolled analysis set, and displays COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

6.4.4.1 ECG Changes from Baseline

Values and changes from baseline in ECG intervals (e.g., RR, QRS, PR, QT, QTcB, QTcF) and ventricular heart rate are also tabulated descriptively as continuous variables at baseline and each scheduled visit in the on-treatment and follow-up safety analysis periods for the safety analysis set.

If there are multiple values on the same acquisition date and time, then the value with the last ECG requisition identifier is used.

6.4.4.2 ECG Interpretation Shifts from Baseline to Worst Category

ECG interpretation shifts from baseline to the worst on-treatment category are tabulated as the number and percentage of subjects with normal, abnormal, and clinically significant abnormal interpretations for the safety analysis set.

6.4.4.3 ECG Abnormalities

On-treatment ECG abnormalities are tabulated as the number and percentage of subjects in the safety analysis set in the categories specified in the Zavegepant Core SAP.

Follow-up ECG abnormalities are tabulated analogously for the follow-up analysis set.

ECG abnormalities are presented together with vital sign and physical measurement abnormalities in the same tables (see Section 6.4.3.2).

6.4.5 S-STS

The S-STS is a prospective rating scale that contains 16 patient-reported questions and 6 clinician-reported questions to track both treatment-emergent suicidal ideation and behaviors.

Refer to the Zavegepant Core SAP for calculation of the S-STS ideation subscale, behavior subscale, and total scores.

Values and changes from baseline in the self-reported S-STS ideation subscale, behavior subscale, and total score are tabulated descriptively as continuous variables at baseline and the worst (highest) score in safety analysis periods. The table also presents the number and percentage of subjects in the worst (highest) score change from baseline category (i.e., < -1, -1,

no change, 1, > 1) in safety analysis periods for the ideation subscale, behavior subscale, and total score.

Results are tabulated on-treatment for the safety analysis set, and follow-up for the follow-up analysis set.

A by-subject listing of S-STS is provided for the enrolled analysis set, and displays COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

Refer to the Zavegepant Core SAP for the listing contents.

6.4.6 Migraine Days per Month

Subjects report migraine status (yes, no, unable to recall) and intensity (mild, moderate, severe, unable to recall) every day in the eDiary evening report. Sites may provide these data on the eDiary medication reconciliation form.

Migraine days per month are assessed as "migraine days per 4 weeks" to correspond with the 4-week visit schedule. Analyses are based on the OP and LTT analysis periods for the migraine analysis set, i.e., subjects in the safety analysis set with ≥ 14 days of data (not necessarily consecutive) in both the OP analysis period and ≥ 1 month (4-week interval) in the LTT analysis period.

- A day of data is defined as an eDiary record with complete date and {yes or no} response to having a migraine. If a subject has multiple responses or migraine severities on the same date, then the most severe migraine last sequenced is chosen. Only days of data are included in analyses.
- A migraine day is defined as a day of data with a "yes" response to having a migraine.
- A treated migraine day is defined as a migraine day on which zavegepant is administered.
- Months are defined as 4-week (28-day) intervals in the LTT analysis period. See Section 6.2.6.1 for the definition of months.

Thus, the total numbers of days of data and migraine days are calculated for the OP analysis period and for each month in the LTT analysis period.

6.4.6.1 Migraine Days per Month over Time

Tables present results separately for the (1) migraine analysis set, and (2) migraine analysis set taking concomitant prophylactic migraine medication (see Section 6.2.5.2).

The number of migraine days per month in the LTT period is examined relative to the number of migraine days per month in the OP by migraine intensity (total [mild, moderate, severe, unable to recall, not reported]; moderate or severe). The following tables are produced:

- Values and changes (both absolute and percent) from the OP in the number of migraine days per month by month during LTT and in the overall LTT summarized descriptively as continuous variables by migraine intensity (including 2-sided 95% normal CIs for mean

change). The number of migraine days per month are prorated to 28 days and derived as follows:

  - OP: 28 × (total number of migraine days in the OP analysis period)/(total number of data days in the OP analysis period).
  - Month during LTT: 28 × (total number of migraine days in the month)/(total number of data days in the month). In addition, subjects must have ≥ 14 days of data (not necessarily consecutive) in a month to be evaluable for that month.
  - Overall LTT: 28 × (total number of migraine days in the LTT analysis period) / (total number of data days in the LTT analysis period).

- Number and percentage of subjects with ≤ 0%, ≥ 25%, ≥ 50%, ≥ 75%, and 100% reduction from the OP in the number of migraine days per month by month during LTT and during overall LTT by migraine intensity.

The following plots are produced for the migraine analysis set:

- Scatter plot of change from OP in the number of total migraine days per month in the overall LTT on the y-axis versus number of total migraine days per month in the OP on the x-axis
- Scatter plot of percent change from OP in the number of total migraine days per month in the overall LTT on the y-axis versus number of total migraine days per month in the OP on the x-axis
- Scatter plot of change from OP in the number of moderate or severe migraine days per month in the overall LTT on the y-axis versus number of moderate or severe migraine days per month in the OP on the x-axis
- Scatter plot of percent change from OP in the number of moderate or severe migraine days per month in the overall LTT the y-axis versus number of moderate or severe migraine days per month in the OP on the x-axis
- Longitudinal plot of mean change from OP in the number of total migraine days per month on the y-axis versus month on the x-axis
- Longitudinal plot of mean change from OP in the number of moderate or severe migraine days per month on the y-axis versus month on the x-axis.

Scatter plots display a horizontal reference line at 0. Longitudinal plots display error bars denoting 95% CIs.

In the percent change/reduction analyses, subjects must also have ≥ 1 migraine day (absolute not prorated) of appropriate migraine intensity during the OP to be included.

A by-subject listing presents migraine attacks and intensity over time for the enrolled analysis set, and displays COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

Another by-subject listing presents the number of migraine days per month during the OP, overall LTT, and by month during the LTT for the safety analysis set.

6.4.6.2 Treated Migraine Days per Month

The number of treated migraine days per month is derived as follows:

- Month during LTT:
  - If the total number of study days in the month < 14: total number of treated migraine days in the month (i.e., no proration)
  - If the total number of study days in the month ≥ 14: 28 × (total number of treated migraine days in the month)/(total number of study days in the month)
- Overall LTT:
  - If the total number of study days in the LTT analysis period < 14: total number of treated migraine days in the LTT analysis period (i.e., no proration)
  - If the total number of study days in the LTT analysis period ≥ 14: 28 × (total number of treated migraine days in the LTT analysis period) / (total number of study days in the LTT analysis period).

All study days from LTT start to LTT end are included in analyses, not only days of data.

The following tables are produced for the safety analysis set:

- Number and percentage of subjects in the following categories based on the number of treated migraine days per month in the overall LTT by migraine intensity (total; moderate or severe): 0, > 0 to < 1, ≥ 1 to < 2, ≥ 2 to < 3, ≥ 3 to < 4, ≥ 4 to < 5, ≥ 5 to < 6, ≥ 6 to < 7, ≥ 7 to < 8, ≥ 8, < 2, ≥ 2. The last 2 categories for total migraine intensity align with subgroups specified in Section 4.3.
- Number and percentage of subjects in the above categories based on the maximum number of treated migraine days per month in any 1 month during LTT by migraine intensity.

These tables are also produced for the safety analysis set with ≥ 51 weeks in the LTT analysis period (see Section 6.2.6.1).

6.4.7 Safety Narratives

A by-subject listing of safety narrative subject identifiers is provided for the following select events, safety analysis periods, and analysis sets as columns:

- Deaths (across all safety analysis periods) for the enrolled analysis set
- SAEs during pre-treatment (only if subject received zavegepant in previous studies BHV3500-201/301), on-treatment, and follow-up for the enrolled analysis set
- AEs leading to discontinuation of study drug (across all safety analysis periods) for the safety analysis set

- On-treatment events of special interest for the safety analysis set:
  - AST or ALT > 3x ULN
  - AST or ALT > 3x ULN concurrent with TBL > 2x ULN
  - TBL > 2x ULN
  - ALP > 2x ULN
  - Select hepatic-related AEs, i.e., PTs containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
  - Local irritation AEs of severe intensity
  - Cardiovascular AEs
  - Suicidality AEs.

Refer to the Zavegepant Core SAP for additional details.

6.5 Outcomes Research

Outcomes research questionnaires and rating scales are MSQ, MIDAS, CGI-c, PoM, and SM. Outcomes research endpoints are assessed for the safety analysis set.

Measurements are first slotted into the pre-LTT, LTT and follow-up analysis periods, and then slotted into analysis visits. If a subject has multiple values in an analysis visit window, then the non-missing value assessed closest to the target date for the visit is used; in the case of a tie, the last value assessed and entered is used. See Sections 6.2.4, 7.2, and 7.3 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

Parameters are summarized at baseline, each scheduled visit, and end of study (EOS), as applicable. EOS is defined as the last non-missing post-baseline value assessed and entered in the study.

By-subject listings of outcomes research questionnaires and rating scales (i.e., MSQ; MIDAS; CGI-c; PoM, and SM) are provided for the enrolled analysis set. All listings except PoM and SM display COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

Refer to the Zavegepant Core SAP for detailed descriptions of these questionnaires and rating scales and listing contents.

6.5.1 MSQ

Impact of treatment on patient-reported quality of life is assessed using the MSQ, which is a 14-item questionnaire that has been validated in migraine patients to assess the effects of migraines on their daily activities over the past 4 weeks. The MSQ is evaluated at the following visits: Pre-Baseline; Weeks 12, 24, 36 and 52; and early termination.

The MSQ consists of the following 3 domains: (1) restrictive role function, (2) preventive role function and (3) emotional function. Values and changes from baseline in transformed scores for each domain are tabulated descriptively as continuous variables (including 2-sided 95% normal CIs for mean change) at baseline, each scheduled post-baseline visit, and EOS. Refer to the Zavegepant Core SAP for deriving transformed scores for each domain.

6.5.2 PoM

The PoM is a 5-point rating scale that measures the patient's preference of study medication to previous medications to treat migraine pain. The PoM is evaluated with the eDiary at early termination and Week 52.

The number and percentage of subjects in each category are tabulated at Week 52 and EOS, including 2-sided exact Clopper-Pearson 95% CIs for each percentage. Refer to the Zavegepant Core SAP for categories.

6.5.3 SM

The SM is a 7-point rating scale that captures the subjects' perception of whether they are satisfied with their headache medication. The SM is evaluated with the eDiary at early termination and Week 52.

The number and percentage of subjects in each category are tabulated at Week 52 and EOS, including 2-sided exact Clopper-Pearson 95% CIs for each percentage. Refer to the Zavegepant Core SAP for categories.

6.5.4 MIDAS

The MIDAS is a retrospective, patient-administered, 5-item questionnaire that measures headache-related disability as lost time due to headache from paid work or school, household work and non-work activities. The MIDAS is evaluated at the following visits: Pre-Baseline; Weeks 12, 24, 36, and 52; and early termination.

Values and changes from baseline in the total, absenteeism, presenteeism, and item scores are tabulated descriptively as continuous variables (including 2-sided 95% normal CIs for mean change) at baseline, each scheduled post-baseline visit, and EOS. Refer to the Zavegepant Core SAP for calculating the total, absenteeism, presenteeism, and item scores.

6.5.5 CGI-c

The CGI-c is an observer-rated 7-point scale that measures patient total improvement relative to the investigator's past experience with other patients with the same diagnosis, with or without collateral information. The CGI-c is evaluated at early termination and the following visits: Weeks 12, 24, 36 and 52.

The number and percentage of subjects in each category are tabulated at each scheduled post-baseline visit and EOS, including 2-sided exact Clopper-Pearson 95% CIs for each percentage. Refer to the Zavegepant Core SAP for categories.

6.6 COVID-19 Impact

Analyses are based on COVID-19 visit impact data with non-missing COVID-19 visit dates (see Section 9.1.1).

Measurements are slotted into analysis periods according to COVID-19 visit dates.

When COVID-19 visit impact is summarized descriptively over time, measurements are first slotted into analysis periods. Next, measurements are slotted into analysis visits in these analysis periods (see Section 7.3).

6.6.1 COVID-19 Overall Impact

COVID-19 overall visit impact is tabulated for the safety analysis set. The number and percentage of subjects in the categories and subcategories defined by COVID-19 visit impact type, COVID-19 visit impact characteristics, and COVID-19 visit impact relationship are tabulated (see Section 9.1.1). In addition, for each of the 3 COVID-19 visit impact type categories (i.e., missed visit; in-person; remote visit), the number and percentage of subjects in the following subcategories defined by the number of visits impacted are tabulated: ≥ 2 visits, …, ≥ 12 visits. Visit counts are based on unique COVID-19 visit dates. Percentages are based on subjects with ≥ 1 visit with non-missing COVID-19 visit impact (see Section 9.1.3).

6.6.2 COVID-19 Impact over Time

COVID-19 visit impact is tabulated at each analysis visit for the safety analysis set. The number and percentage of subjects in the categories and subcategories defined by COVID-19 visit impact type, visit impact characteristics, and visit impact relationship are presented for each analysis period (pre-LTT, LTT, follow-up) and analysis visit. Percentages are based on subjects with ≥ 1 visit with non-missing COVID-19 visit impact in the analysis visit window.

Missing LFT data impacted by COVID-19 are tabulated at each analysis visit for the safety analysis set as the number and percentage of subjects in the following categories:

1) Missing LFT data, defined as missing values for all of the 4 following LFTs in the analysis visit window: ALT, AST, ALP, and TBL.
2) Missing LFT data at visits impacted by COVID-19, i.e., meeting criteria (1) and having ≥ 1 visit impacted by COVID-19 in the analysis visit window (see Section 9.1.3)
3) Missing LFT data at missed visits due to COVID-19, i.e., meeting criteria (1), (2), and having ≥ 1 missed visit in the analysis visit window (see Section 9.1.1).

Percentages are based on evaluable subjects at each analysis visit in each analysis period (pre-LTT, LTT, follow-up). A subject is evaluable at an analysis visit during pre-LTT or LTT if the study day corresponding to the last contact date is ≥ lower bound of the analysis visit window. A subject is evaluable at an analysis visit during follow-up if the follow-up day corresponding to the last contact date is ≥ lower bound of the analysis visit window. See Section 7.1 for derived dates, and Section 7.3 for study days and follow-up days.

6.6.3 COVID-19 Listings

A by-subject listing of COVID-19 impact codes by visit displays visits with abbreviated labels (e.g., SCR=Screening in pre-LTT, W12=Week 12 in LTT; FU2=Follow-up Week 2) in separate columns for the enrolled analysis set. Spanning headers above the visits display the analysis period (pre-LTT, LTT, or follow-up). Each column denotes an analysis visit in Table 3 and displays the COVID-19 visit impact code (see Section 9.1.5.1). If a subject has multiple COVID-19 visit impact codes in an analysis visit window, then results are displayed sorted by visit date and comma-concatenated across all COVID-19 visit dates in the analysis visit window (e.g., "#,&UM1" if "#" has visit date of 01JUL2020 and "&UM1" has visit date of 10JUL2020). Visits during the on-treatment safety analysis period are identified. Footnotes describe the abbreviations in the COVID-19 visit impact code (see Section 9.1.5.2).

A by-subject listing of COVID-19 visit impact is provided for the enrolled analysis set (see Section 9.1.1). The listing displays analysis period, analysis visit, COVID-19 visit date, study day derived from COVID-19 visit date, treatment day derived from COVID-19 visit date, visit type (scheduled or unscheduled), visit impact type, visit impact characteristics, visit impact relationship with specify text, and premature study termination (yes; no; not applicable).

7 CONVENTIONS

7.1 Derived Dates

Derived dates for defining analysis periods are defined as follows:

- Study drug date/time: Complete finding date/time corresponding to "yes" response to question about taking study medication and number of sprays > 0 in the eDiary evening report or medication reconciliation form.

- Study drug start date/time: Earliest study drug date/time.

- Study drug end date/time: Latest study drug date/time.

- Study drug last date/time: Study drug end date/time derived only for subjects with non-missing response to the question "Did the subject complete the study?" on the Study Exit Status CRF. Thus, in an interim analysis, all post-baseline data are included for a subject who is still on study. At the last database lock, the study drug last date is equal to the study drug end date.

- LTT start date/time: Earlier of (1) study drug start date/time, and (2) IWRS baseline visit date (i.e., Baseline/Day 1 visit date from the BHV3500_202 IWRS Visit Report csv file).

- LTT end date/time: Later of (1) latest complete finding date/time in the eDiary on or after the LTT start date/time, and (2) latest complete visit date on or after the LTT start date through the Week 52/Early Termination visit date, and excluding the Follow-up Week 2 visit date, from the Visit Date CRFs.

- LTT last date/time: LTT end date/time derived only for subjects with non-missing response to the question "Did the subject complete the study?" on the Study Exit Status CRF. Thus, in an interim analysis, all LTT data are included for a subject who is still on study. At the last database lock, the LTT last date is equal to the LTT end date.

- OP start date/time: Earliest complete finding date/time in the eDiary before the LTT start date/time.

- OP end date/time: Latest complete finding date/time in the eDiary before the LTT start date/time.

- COVID-19 visit date: (1) Complete visit date, if it exists; (2) otherwise, complete date the visit was planned to occur for a missed visit (see Section 9.1.1).

- Last contact date: (1) Earliest complete death date from the AE CRF, if it exists; (2) otherwise, the maximum complete date of the following: AE start or stop; COVID-19 visit only for in-person or remote visits; ECG; eDiary finding; informed consent; IWRS baseline visit; laboratory test collection; nasal inspection; non-study medication start or stop; physical exam; physical measurement; procedure; rating scale; questionnaire; vital sign; visit. If the last contact date is after the most recent raw database creation date, then it is set to the most recent raw database creation date.

- Death date: Last contact date derived only for subjects who died (see Section 6.4.1).

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

7.2 Analysis Periods

Analysis periods are defined as follows:

- OP: measurement date/time on or after the OP start date/time through the OP end date/time. This period is used to assess the number of migraine days per month during the OP.

- Pre-treatment: measurement date/time on or before the study drug start date/time. This period is used to derive baseline values, and to assess safety and outcomes research endpoints. Note that all measurements are pre-treatment for subjects in the enrolled analysis set with missing study drug start date.

- Pre-LTT: measurement date/time on or before the LTT start date/time. This period is used to derive analysis visit windows for slotting observations. Note that all measurements are pre-LTT for subjects in the enrolled analysis set with missing LTT start date.

- LTT: measurement date/time after the LTT start date/time through the LTT last date. This period is used to derive analysis visit windows for slotting observations, and to assess exposure and migraine days during LTT. Note that AEs with imputed start date equal to the

LTT start date are part of this period (refer to the Zavegepant Core SAP for AE start date imputation).

- Follow-up: measurement date after the LTT last date. This period is used to slot observations.

- On-treatment safety: measurement date/time after the study drug start date/time through the study drug last date + 7 days. This period is used to assess safety endpoints on treatment. Note that AEs with imputed start date equal to the study drug start date are part of this period.

- Follow-up safety: measurement date after the study drug last date + 7 days. This period is used to assess safety endpoints during follow-up.

See Section 7.1 for derived dates for determining analysis periods. If measurement time is missing, not collected, or not applicable for a parameter, then the measurement date is compared to the derived date.

7.3 Analysis Visit Windows

Refer to Protocol Section 4.3 for the schedule of assessments.

Study days are calculated from the LTT start date as follows:

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

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

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

Follow-up days are calculated from the LTT last date as follows:

- Measurement date – LTT last date, if measurement date ≥ LTT last date + 1
- Measurement date – LTT last date – 1, if measurement date < LTT last date + 1

Evaluation intervals are based on study days in the LTT analysis period and follow-up days in the follow-up analysis period (see Section 7.2). Table 3 presents analysis visit windows.

Table 3: Analysis Visit Windows

Analysis Period Analysis Visit	Abbreviation in Listings	Analysis Day Analysis-specified Interval	Target Day
Pre-LTT	**PRELTT**	**Study Day**	
Screening		≤ -6 or missing	
Pre-Baseline	Prebaseln	-5 to -1	
Baseline		1	
LTT	**LTT**	**Study Day**	
Week 2		1 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12		71 to 98	84
Week 16		99 to 126	112
Week 20		127 to 154	140
Week 24		155 to 182	168
Week 28		183 to 210	196
Week 32		211 to 238	224
Week 36		239 to 266	252
Week 40		267 to 294	280
Week 44		295 to 322	308
Week 48		323 to 350	336
Week 52		351 to 378	364
Extension *	Ext	≥ 379	
Follow-up	**FU**	**Follow-up Day**	
Follow-up Week 2	FU Week 2	1 to 21	14
Follow-up Extension *	FU Ext	≥ 22	

* Denotes an extended visit in the analysis period and is displayed primarily in listings

Note that the baseline analysis visit in Table 3 is independent of the baseline value for a parameter defined in Section 6.2.5. The former is used only in by-subject listings that display visit and in COVID-19 analyses by analysis visit (see Sections 6.6.2 and 6.6.3).

7.4 Duplicate Subjects

If the same subject is treated in the study more than once and is assigned more than 1 subject identifier (see Section 9.2), then the following conventions apply to analyses:

- Pre-treatment derived dates (i.e., OP start/end dates, LTT start date, study drug start date) are derived using data only from the subject identifier corresponding to the first treatment.

- All other derived dates (i.e., LTT end/last date, study drug end/last date, last contact date) are derived using data from all duplicate subject identifiers.
- Baseline characteristics excluding non-study prior medications are assessed using data only from the subject identifier corresponding to the first treatment.
- Protocol deviations, non-study prior medications, exposure, safety, migraine days, and outcomes research endpoints are assessed comprehensively using data from all duplicate subject identifiers.
- Subject disposition during treatment table displays study exit status data from the last duplicate subject identifier.
- Listings of subject disposition, protocol deviations, safety, exposure, migraine days, and outcomes research displays data from all duplicate subject identifiers under the subject identifier corresponding to the first treatment.

8 CONTENT OF REPORTS

An interim CSR is produced to support the intranasal zavegepant new drug application submission. All TLFs described in this SAP are produced for the interim CSR, except those for the migraine analysis set, exploratory endpoint of migraine days per month, and the subgroup of total treated migraine days per month in the overall LTT (see Sections 4.1, 4.3, and 6.4.6).

The final CSR is produced after the final data base lock, which occurs after the last subject reaches Follow-up Week 2. All TLFs described in this SAP are produced for the final CSR.

9 APPENDICES

9.1 COVID-19 Visit Impact

Analyses are based on the COVID-19 Visit Impact CRF.

9.1.1 COVID-19 Visit Impact CRF Description

At each visit (scheduled or unscheduled), sites complete the COVID-19 Visit Impact CRF.

Unscheduled visits are identified from visit labels containing “unscheduled”. Otherwise, all other visits are considered scheduled. In listings, the COVID-19 visit type is abbreviated as “U” for unscheduled visits and blank (i.e., missing) otherwise.

COVID-19 visit impact status is based on the response to the lead question “Was this visit impacted by COVID-19 related issues? (yes or no)”. In listings, the COVID-19 visit impact status is abbreviated as “&” for yes and “#” for no.

If the response to the lead question is "yes", then responses to the following questions are provided:

- COVID-19 visit impact type: What was the impact? (indicate one)
  - (1) Missed visit – no assessments done [abbreviated COVID-19 impact type = "M" in listings]
    - Date visit planned to occur [used to derive the COVID-19 visit date]
  - (2) In-person visit at site (check all that apply) [abbreviated COVID-19 impact type = "I" in listings]
    - Not all assessments completed [abbreviated as "N" in listings] *
    - Scheduled visit occurring earlier or delayed relative to protocol specified schedule [abbreviated as "S" in listings] *
  - (3) Remote visit (indicate one) [abbreviated as "R" in listings]
    - Virtual visit (video/telemedicine) [abbreviated as "V" in listings] *
    - Telephone contact [abbreviated as "T" in listings] *

  Subcategories marked with "*" are visit impact characteristics.
- COVID-19 visit impact relationship: How was the impact related to COVID-19? (check all that apply)
  - Subject diagnosed with COVID-19 or quarantined due to COVID-19 [abbreviated as "1" in listings]
  - Site closed or access restricted due to COVID-19 [abbreviated as "2" in listings]
  - Site open but subject unwilling or unable to come to the site due to COVID-19 [abbreviated as "3" in listings]
  - Other [abbreviated as "4" in listings], with specify text
- COVID-19 premature study termination: If the subject is terminating the study prematurely, was the termination related to COVID-19? (yes; no; not applicable) [abbreviated as "X" for yes, "Z" for no, and blank otherwise in listings].

9.1.2 COVID-19 Impact

A subject is impacted by COVID-19 if there is a "yes" response to the lead question at ≥ 1 visit.

9.1.3 COVID-19 Visit Impact

A visit is impacted by COVID-19 if there is a "yes" response to the lead question at that visit (see Section 9.1.1).

A visit is not impacted by COVID-19 if there is a "no" response to the lead question at that visit.

9.1.4 COVID-19 Premature Study Termination

A subject terminated the study prematurely due to COVID-19 if all of the following criteria are met: "yes" response to the COVID-19 premature study termination question at ≥ 1 visit (see Section 9.1.1); did not complete the study (see Section 6.2.3). Reasons for premature termination are based on the reasons for early discontinuation (i.e., not completing the study).

9.1.5 COVID-19 Visit Impact Code

9.1.5.1 COVID-19 Visit Impact Code Derivation

At each visit, the COVID-19 visit impact code is derived as follows:

- If the visit is impacted by COVID-19, then the value is the concatenation of the COVID-19 abbreviations described in Section 9.1.1 in the following order:
  1) Visit impact status (i.e., lead question response): "&"
  2) Visit type: "U" if unscheduled
  3) Visit impact type: "M", "I", or "R"
  4) Visit impact characteristics: "N", "S", "T", or "V". Both "N" and "S" may be selected for in-person visits.
  5) Visit impact relationship: 1, 2, 3, or 4. Multiple responses may be selected.
  6) Premature study termination: "X" or "Z".

  Examples:
  - "&UINS24X" if visit type is unscheduled, visit impact type is in-person visit, visit impact characteristics are "Not all assessments completed" and "Scheduled visit occurring earlier or delayed relative to protocol specified schedule", visit impact relationships are "Site closed or access restricted due to COVID-19" and "Other", and premature study termination is yes.
  - "&RT1" if visit type is scheduled, visit impact type is remote visit, visit impact characteristic is "Telephone contact", visit impact relationship is "Subject diagnosed with COVID-19 or quarantined due to COVID-19", and premature study termination is not applicable.
- If the visit is not impacted by COVID-19, then the value is the concatenation of the visit impact status "#" and the visit type ("U" if unscheduled).
- Otherwise, the value is blank (i.e., missing).

9.1.5.2 COVID-19 Visit Impact Code in Listings

Select by-subject listings of measurements over time display all COVID-19 visit impact codes for visits impacted by COVID-19 as additional data records (see Section 9.1.3). Refer to the Mock TLF CSR document for more details.

COVID-19 measurements are slotted into analysis periods and analysis visit windows according to the COVID-19 visit date (see Sections 7.1 through 7.3).

In the listing of COVID-19 impact codes by visit, footnotes describe the abbreviations in the COVID-19 visit impact code, e.g., "COVID-19 visit impact code: & = Impacted; # = Not impacted; I = In-person visit at site; M = Missed visit; N = Not all assessments done; R = Remote visit; S = Scheduled visit early or late; T = Telephone; U = Unscheduled; V = Virtual; X = Premature termination due to COVID-19; Z = Premature termination not due to COVID-19; 1 = Subject dx or quar.; 2 = Site closed or restricted access; 3 = Site open but subject unwilling/unable to come to site; 4 = Other".

9.2 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- LTT participated or treated with study drug more than once and assigned > 1 subject identifier. These subjects are identified from the protocol deviation CTMS file.
- < 2 migraines attacks treated with migraine standard of care medication during the Observation Phase based on the eDiary evening report. Defined as a total of 0 or 1 day in the OP analysis period in which there were "yes" responses to the 2 questions about having a migraine headache and taking any medication other than study medication to treat the migraine headache in the eDiary evening report on the same day.
- Cardiovascular disease risk factor, defined as any of the following subcategories:
    - Ischemic coronary artery disease
    - Other significant underlying cardiovascular disease
    - Coronary artery vasospasm including Prinzmetal's angina
    - Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders
    - Other arrhythmias
    - History of stroke or transient ischemic attack
    - Peripheral vascular disease
    - Ischemic bowel disease
    - Uncontrolled hypertension

  These are identified from "yes" responses to having risk factors listed above on the Cardiac and Other Risk Factors CRF. Only subcategories with "yes" responses are presented.
- Medical history, defined as any of the following subcategories:
    - Basilar migraine or hemiplegic migraine
    - Active chronic pain syndrome or other pain syndromes other than migraine
    - Dementia or significant neurological disorder other than migraine

- Major depressive disorder with atypical antipsychotics taken during pre-LTT, schizophrenia, bipolar disorder, or borderline personality disorder. PTs must contain any of the following: major depress; schizophrenia; bipolar disorder; borderline personality disorder. Refer to the Zavegepant Core SAP for atypical antipsychotics.
- Gilbert's syndrome or any other active hepatic or biliary disorder.

For each subcategory, PTs are displayed alphabetically as additional subcategories. Unless specified otherwise, PTs are identified by the Biohaven medical lead or designee from reviewing a list of unique medical history SOC and PTs.

- Finding out of range, defined any as any of the following subcategories:
  - Females with a positive pregnancy test on or after informed consent (see Section 6.4.2)
  - Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 mL/min/1.73m^2 during pre-LTT *
  - BMI ≥ 33 kg/m^2 during pre-LTT *
  - S-STS total score > 0 during pre-LTT.

  For the subcategories marked with "*", all non-missing values during the pre-LTT analysis period must meet the deviation criteria in order to be considered a deviation.

Relevant subject management protocol deviations include the following categories:

- Study drug dosing error, defined as any of the following subcategories:
  - Study drug taken but not participated in the LTT phase
  - Administered > 1 spray on any 1 day (see Section 6.2.6.1)
  - Administered > 8 sprays per month in any 1 month (see Section 6.2.6.1).
- eDiary site or subject usage compliance < 80% from LTT start to end (see Section 6.2.6.2)
- Prohibited non-study medications, defined as any of the following subcategories:
  - Atypical antipsychotics, divalproex, valproic acid, or valproate taken on or after informed consent #
  - Barbiturate taken up to 14 days before LTT start or afterward #
  - Butterbur root or extract taken up to 14 days before LTT start or afterward
  - Ergotamine, lasmitidan, or triptan taken up to 2 days before LTT start or afterward #
  - Gepant taken on or after informed consent #
  - Lamotrigine taken on or after informed consent
  - Medication administered nasally (1) anytime during pre-LTT, or (2) for ≥ 10 days (not necessarily consecutive) per month on or after LTT start #. Route must be nasal. For criterion (2), the following applies:

- Analyses are similar to study drug exposure in which results are not prorated to 28 days (see Section 6.2.6.1). However, analyses are based on all months (4-week intervals) during the LTT and follow-up analysis periods combined. Meeting the criteria in ≥ 1 month (4-week interval) is considered a deviation. Days in which medication is taken are determined using imputed medication start and stop dates across all records with nasal route. If the frequency is at least QD (i.e., QD, BID, TID, QID, QM, or QHS), then all days in the specified time period that are between the imputed start date and imputed stop date inclusive count. If the frequency is PRN, then all days in the specified time period that are equal to the imputed start date or imputed stop date count. If the frequency is other, then all days in the specified time period that are equal to the imputed medication start date count.

- Muscle relaxant (excluding baclofen) taken on or after LTT start #
- Narcotic taken up to 2 days before LTT start or afterward #
- Select strong cytochrome P450 3A4 (CYP3A4) inducers taken up to 14 days before study drug #. These are non-study medications with (1) study drug date – 14 ≤ imputed start or imputed stop date ≤ study drug date, or (2) imputed start date ≤ study drug date – 14 < study drug date ≤ imputed stop date. All study drug dates are considered.
- Select strong CYP3A4 inhibitors taken up to 14 days before study drug #.

For the subcategories marked with "#", preferred names are displayed alphabetically as additional subcategories. See Section 6.2.5.4 for the definition of medication taken during pre-LTT. See Section 6.2.6.3 for the definition of medication taken on or after LTT start. Medications taken up to *X* days before a reference date or afterward are defined as those with imputed medication start date or imputed stop date ≥ reference date – *X*. Refer to the Zavegepant Core SAP for additional details about prohibited non-study medications.

10 REFERENCES

Not applicable.