PROTOCOL TITLE: BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine

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Biohaven Pharmaceuticals

Protocol BHV3500-301

BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) intranasal (IN) for the Acute Treatment of Migraine

Statistical Analysis Plan

Version 5.0

Date: 15-Sep-2021

SIGNATURE PAGE

Protocol Title: BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) intranasal (IN) for the Acute Treatment of Migraine

Sponsor: Biohaven Pharmaceuticals, Inc.

Document Version: 5.0

Date: 15-Sep-2021

Author: PPD PPD PPD
Biohaven Pharmaceuticals

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 are described in the Clinical Study Report (CSR).

Sponsor Signatories:

PPD PPD
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Biohaven Pharmaceuticals

Signature:_____

Date:_____

PPD PPD
PPD Biohaven
Pharmaceuticals

Signature:_____

Date:_____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

REVISION HISTORY

Version	Description of Change
1.0	Original issue based on Protocol Version 2.0 (22-Sep-2020)
2.0	Based on Protocol Version 2.0 (22-Sep-2020). General: Applied standards from the Biohaven Style Guide. Changed "eCRF" to "CRF". Abbreviations: Added CK and CYP3A4. Replaced eCRF with CRF. Section 3.2.3: In Table 3, specified the analysis set in the "Summary" rows instead of the "Endpoint" rows, and replaced the outcomes research analysis set with the efficacy 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. Section 6.2.5: Specified the meaning of "last" for deriving baseline. Section 6.2.3.4: New section "Overall Premature Study Termination due to COVID-19". Moved relevant text from Section 6.2.3.3 here. Section 6.2.6.2: Specified linkage to medical history and AE CRFs. Section 6.4: Referenced the Zavegepant Core SAP about slotting safety parameters into analysis periods. Section 6.4.1.1: New section "Deaths". Added a table of deaths. Specified the contents of the deaths listing. Section 6.4.1.2: Removed death from and added AEs of special interest to the AE overview table. 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 efficacy analysis set. Section 7.1: Modified the derivation of the last contact date. Section 7.2: Specified that all measurements are pre-treatment for subjects in the enrolled analysis set with missing study drug start date, and that the on-treatment period is used to assess safety endpoints on treatment. Section 9.2: Added select CYP3A4 inducers and inhibitors.
3.0	Based on Protocol Version 2.0 (22-Sep-2020). Signature page: Replaced PPD with PPD Abbreviations: Added CTMS. General: Fixed hyperlinks throughout. Section 2.4: Specified that SAP Versions 1.0, 2.0, and 3.0 are based on Protocol Version 2.0. Section 4.3: Removed the "Non-study stable prophylactic migraine medication use through randomization" subgroup. Section 6.1.1.2: Specified that select listings display COVID-19 visit impact code for visits that are impacted by COVID-19. Sections 6.2.1 and 6.2.2: Changed "randomized" to "full". Section 6.2.4.1: New section "Relevant Protocol Deviations". Moved text from Section 6.2.4 here. Changed the listing to be on the enrolled analysis set. Section 6.2.4.2: New section "Significant Protocol Deviations". Added a listing of significant

Version	Description of Change
	protocol deviations. Sections 6.3.1.1 and 6.3.1.2: Specified that response rates by treatment group are not stratified. Changed "overall response" to "response". 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: Changed "local laboratory CK fractionation" to "CK elevation questionnaire". Section 6.4.6: Removed "Local irritation AEs of severe intensity". Section 7.1: Modified the derivation of the last contact date. Section 7.3: Removed the last paragraph. Section 9.2: • Replaced deviation for previous enrollment in any BHV3500 study with previously treated with study drug in another BHV3500 study. • Added deviation for (1) randomized or treated with study drug more than once and assigned > 1 subject identifier, and (2) prophylactic migraine medication started or stopped from 3 months before informed consent to randomization. • Removed deviations for elevated HbA1c, systolic blood pressure, and diastolic blood pressure through randomization. • Replaced "at any time during the study" or "any time during the study" with "on or after informed consent" throughout. • Specified that the IWRS randomization date is the reference date for "randomization", and if the IWRS randomization date is missing, then the study drug start date is used.
4.0	Based on Protocol Version 4.0 (02-Jun-2021). Section 2.4: Specified that SAP Version 4.0 is based on Protocol Version 4.0. Section 6.2.3: Modified the subject disposition listing to include previous subject identifier. Section 7.4: New section "Duplicate Subjects". Section 7.5: Renumbered previous eDiary section 7.4 and subsections accordingly. Section 9.2: Changed "BMI ≥ 35" to "BMI ≥ 40".
5.0	Based on Protocol Version 4.0 (02-Jun-2021). Section 2.4: Specified that SAP Version 5.0 is based on Protocol Version 4.0. Section 6.2.5: Removed reference to the central laboratory. Specified to see Sections 6.4.2.3, 6.4.3.1, and 6.4.4.1 for handling of ties on the same measurement date or time. Section 6.3.4.4: New section "Efficacy Endpoints Compared over Time". Section 6.4: Modified algorithm for selecting a safety parameter value in the end of treatment 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 in the end of treatment 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).

Version	Description of Change
	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 date and time by the external source CCI
	Section 6.4.4.1: Specified the handling of ties on the same measurement date and time.
	Section 6.4.6: Changed “AST or ALT” to “ALT or AST”.
	Section 7.1: Modified the derivation of study drug start date/time.
	Section 7.4: Specified that the unique subject identifier is derived as per latest version of Biohaven Dataset Guidelines. Replaced “randomized or treated” with “full analysis set”.
	Section 7.5.1.1: Specified that the eDiary Migraine Report collects study medication dose date or time based on when the subject reported taking study medication (today, yesterday, or other).
	Section 9.2: Added a protocol deviation for BMI ≥ 35 and consented to Protocol Version 3 or lower. Specified consent to Protocol Version 4 for BMI ≥ 40.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASE	Asymptotic standard error
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
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
FCS	Fully conditional method
IN	Intranasal
IP	Investigational product
IWRS	Interactive web response system
LFT	Liver function test
MBS	Most bothersome symptom
MDRD	Modification of diet in renal disease
MQoL	Migraine Specific Quality of Life Questionnaire
NC=F	Non-Completer = Failure
NC1=F	Non-Completer with Missing Data at More than 1 Time Point = Failure
NC=M	Non-Completer = Missing
NSAID	Non-steroidal anti-inflammatory drug
PID	Patient identifier
PoM	Preference of medication
PT	Preferred term
RM=F	Rescue Medication = Failure
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TBL	Total bilirubin
TLF	Table listing figure
UDS	Unit dose system

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (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 CSR.

1.1 Research Hypothesis

Zavegepant will have efficacy superior to placebo in the treatment of acute migraine with a favorable safety profile suitable for use by a broad subject population.

1.2 Schedule of Analyses

All analyses described in this SAP are performed after the last subject completes the end of treatment visit or discontinues from the study, and the database has been locked. No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

BHV3500-301 is a Phase 3, double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of zavegepant versus placebo in the treatment of moderate or severe migraine.

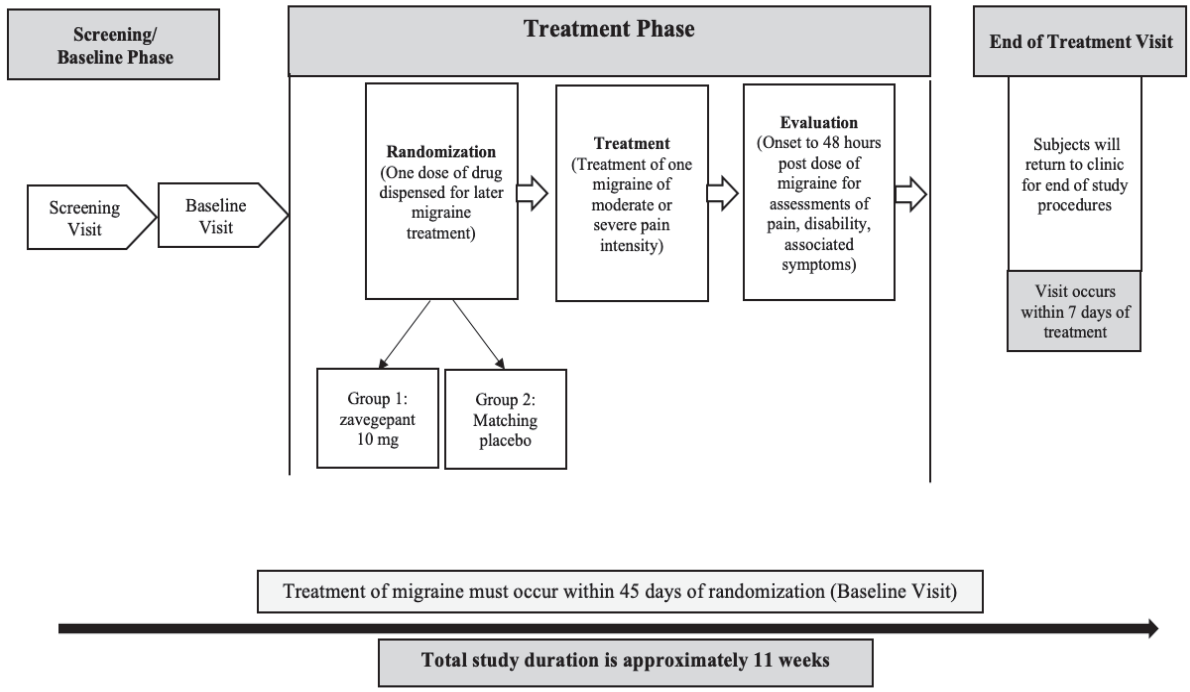
The design of the study is shown in Figure 1. After providing informed consent, subjects first participate in the screening phase (28-day period) to determine eligibility for the study. Approximately 1,750 subjects are screened to randomize approximately 1,400 subjects to study medication (zavegepant or placebo). The study drug zavegepant (BHV-3500) is formulated as 10 mg intranasal (IN) or matching placebo. Randomization is stratified by IWRS prophylactic migraine medication use (yes or no).

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

After randomization, study medication is dispensed to subjects to take home for up to 45 days. Subjects are dispensed one Aptar Unit Dose System (UDS) liquid spray device containing a single dose of study medication zavegepant or a matching placebo. Subjects are instructed to take their study medication as an outpatient, when they have a migraine headache which reaches moderate or severe pain intensity. Subjects are instructed by an electronic diary (eDiary) to take study medication after a migraine attack of moderate or severe pain intensity. Subjects complete an eDiary for up to 48 hours after taking the study medication. Subjects also record efficacy and outcomes research data in their eDiary.

Subjects return to the study site within 7 (± 2) days of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety. If a subject has NOT experienced a migraine headache of moderate or severe pain intensity within 45 days after randomization, they still are required to complete all EOT visit procedures and return unused study medication and eDiary to the investigational site.

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 a randomized treatment group (zavegepant or placebo) using permuted blocks of size 4 within each prophylactic migraine medication use randomization stratum (yes or no). The IWRS also assigns specific container numbers for all blinded study drug to be dispensed.

2.3 Blinding and Unblinding

This study is blinded through the final data base lock (see Section 1.2). Draft TLFs produced prior to data base lock are produced with dummy treatment groups.

2.4 Protocol and Protocol Amendments

BHV3500-301 SAP Versions 1.0, 2.0, and 3.0 are based on BHV3500-301 Protocol Version 2.0. BHV3500-301 SAP Versions 4.0 and 5.0 are based on BHV3500-301 Protocol Version 4.0.

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objectives

To compare the efficacy of zavegepant with placebo in the acute treatment of migraine, as measured by co-primary endpoints of pain freedom at 2 hours postdose, and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose.

3.1.2 Secondary Objectives

1. To compare zavegepant with placebo for pain relief at 2 hours postdose.
2. To compare zavegepant with placebo for return to normal function at 2 hours postdose according to the Functional Disability scale.
3. To compare zavegepant with placebo for sustained pain relief from 2 to 24 hours postdose.
4. To compare zavegepant with placebo for sustained pain relief from 2 to 48 hours postdose.
5. To compare zavegepant with placebo for sustained pain freedom from 2 to 24 hours postdose.
6. To compare zavegepant with placebo for sustained pain freedom from 2 to 48 hours postdose.
7. To compare zavegepant with placebo for phonophobia freedom at 2 hours postdose.
8. To compare zavegepant with placebo for photophobia freedom at 2 hours postdose.
9. To compare zavegepant with placebo for pain relief at 60 minutes postdose.
10. To compare zavegepant with placebo for return to normal function at 60 minutes postdose according to the Functional Disability scale.
11. To compare zavegepant with placebo for pain relief at 30 minutes postdose.
12. To compare the zavegepant with placebo for return to normal function at 30 minutes postdose according to the Functional Disability scale.
13. To compare zavegepant with placebo for pain relief at 15 minutes postdose.
14. To compare zavegepant with placebo for return to normal function at 15 minutes postdose according to the Functional Disability scale.
15. To compare zavegepant with placebo for rescue medication use within 24 hours postdose.
16. To compare zavegepant with placebo for nausea freedom at 2 hours postdose.
17. To compare zavegepant with placebo for pain relapse from 2 to 48 hours postdose.

3.1.3 Exploratory Objectives

1. To evaluate zavegepant relative to placebo for pain freedom at all scheduled time points postdose.
2. To evaluate zavegepant relative to placebo for pain relief at all scheduled time points postdose.
3. To evaluate zavegepant relative to placebo for freedom from MBS at all scheduled time points postdose.
4. To evaluate zavegepant relative to placebo for return to normal function at all scheduled time points postdose.
5. To evaluate zavegepant relative to placebo for phonophobia freedom at all scheduled time points postdose.
6. To evaluate zavegepant relative to placebo for photophobia freedom at all scheduled time points postdose.
7. To evaluate zavegepant relative to placebo for nausea freedom at all scheduled time points postdose.
8. To evaluate zavegepant relative to placebo for the Migraine Quality of Life Questionnaire (MQoL).
9. To evaluate zavegepant relative to placebo for the Preference of Medication (PoM).
10. To evaluate the safety and tolerability of zavegepant in the acute treatment of migraine, as measured by the frequency of adverse events of moderate or severe intensity, serious adverse events, clinically relevant laboratory test abnormalities, and nasal inspection abnormalities.
11. To evaluate zavegepant relative to placebo for the Sheehan-Suicidality Tracking Scale (S-STS).

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.

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

Intercurrent Events

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

For efficacy objectives, intercurrent events are handled with a composite strategy, i.e., the occurrence of the intercurrent event is integrated as a component of the endpoint. See Section 6.3 for additional details.

For safety and outcomes research objectives, intercurrent events are 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 rescue medication use.

Data Sources for Endpoints

The following are from the eDiary: migraine characteristics (i.e., pain, MBS, nausea, phonophobia, photophobia, and functional disability); study medication; MQoL; and PoM.

Rescue medication use is from the Rescue Medication case report form (CRF).

AEs are from AE CRFs.

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

S-STS scores are derived from the S-STS CRF.

3.2.1 Primary Objective Estimands

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

For each objective, intercurrent events are handled with a composite strategy described in Section 3.2. Subjects who take rescue medication at or before 2 hours postdose are classified as failures (see Section 6.3). Subjects with missing data at 2 hours postdose are considered failures for the main estimand, whereas they are excluded for the sensitivity estimand (see Section 6.3).

For each objective, the summary is the difference in the percentage of subjects achieving the endpoint response criteria between the zavegepant and placebo treatment groups using the efficacy analysis set.

Table 1: Co-Primary Objective Estimands

Objective **Efficacy Endpoint**	**Pain freedom at 2 hours postdose** Percentage of subjects with pain intensity of none at 2 hours postdose. Pain intensity is measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe).
Objective **Efficacy Endpoint**	**MBS freedom at 2 hours postdose** Percentage of subjects with MBS reported on study before dosing that is absent at 2 hours postdose. The MBS on study before dosing is reported as nausea, phonophobia, or photophobia. Symptom status is reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).

3.2.2 Secondary Objective Estimands

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

For each endpoint except rescue medication use within 24 hours postdose, intercurrent events are handled with a composite strategy described in Section 3.2. Subjects who take rescue medication are classified as failures for all efficacy assessments that are reported at or after taking rescue medication (see Section 6.3).

For each objective, the summary is the difference in the percentage of subjects achieving the endpoint response criteria between the zavegepant and placebo treatment groups using the efficacy analysis set.

Table 2: Secondary Objective Estimands

Objective **Efficacy Endpoint**	**Pain relief at 15 minutes, 30 minutes, 60 minutes, and 2 hours postdose** At each specified time point, percentage of subjects with a pain intensity of none or mild at time point
Objective **Efficacy Endpoint**	**Return to normal function at 15 minutes, 30 minutes, 60 minutes, and 2 hours postdose** At each specified time point, percentage of subjects with a functional disability level of normal at the time point; evaluated for subjects with functional disability at the time of dosing. Functional disability level is measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest), and functional disability are defined as mildly impaired, severely impaired, or requires bedrest.
Objective **Efficacy Endpoint**	**Sustained pain relief from 2 to 24 hours postdose, and 2 to 48 hours postdose** Percentage of subjects with pain intensities of none or mild at all time points from the start to the end of the time period of interest
Objective **Efficacy Endpoint**	**Sustained pain freedom from 2 to 24 hours postdose, and from 2 to 48 hours postdose** Percentage of subjects with pain intensities of none at all time points from the start to the end of the time period of interest
Objective **Efficacy Endpoint**	**Phonophobia freedom at 2 hours postdose** Percentage of subjects with phonophobia absent at 2 hours postdose; evaluated for subjects with phonophobia present at the time of dosing
Objective **Efficacy Endpoint**	**Photophobia freedom at 2 hours postdose** Percentage of subjects with photophobia absent at 2 hours postdose; evaluated for subjects with photophobia present at the time of dosing

Objective	**Rescue medication use within 24 hours postdose**
Efficacy Endpoint	Percentage of subjects taking rescue medication within 24 hours postdose
Intercurrent Events	Not applicable (intercurrent event is the endpoint)
Objective	**Nausea freedom at 2 hours postdose**
Efficacy Endpoint	Percentage of subjects with nausea absent at 2 hours postdose; evaluated for subjects with nausea present at the time of dosing
Objective	**Pain relapse from 2 to 48 hours postdose**
Efficacy Endpoint	Percentage of subjects with a pain intensity of mild, moderate, or severe at any time point after 2 hours postdose; evaluated for subjects with pain freedom at 2 hours postdose

3.2.3 Exploratory Objective Estimands

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

For each efficacy objective, intercurrent events are handled with a composite strategy described in Section 3.2. Subjects who take rescue medication are classified as failures for all efficacy assessments that are reported at or after taking rescue medication (see Section 6.3).

For efficacy endpoints, subjects with missing data at a time point are considered failures for the main estimand, whereas they are excluded for the sensitivity estimand (see Section 6.3).

Table 3: Exploratory Objective Estimands

Objective	**Pain freedom at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with a pain intensity of none at the time point
Summary	Percentage of subjects with pain freedom over time by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**Pain relief at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with a pain intensity of none or mild at the time point
Summary	Percentage of subjects with pain relief over time by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**MBS freedom at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with MBS reported on study before dosing that is absent at the time point
Summary	Percentage of subjects with MBS freedom over time by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**Return to normal function at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with a functional disability level of normal at the time point for the subset with functional disability (mildly impaired, severely impaired, or requires bedrest) at the time of dosing
Summary	Percentage of subjects with return to normal function over time by treatment group for the efficacy analysis set

Objective	**Pain freedom at all time points postdose**
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**Phonophobia freedom at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with phonophobia absent at the time point for the subset with phonophobia present at the time of dosing
Summary	Percentage of subjects with phonophobia freedom over time by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**Photophobia freedom at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with photophobia absent at the time point for the subset with photophobia present at the time of dosing
Summary	Percentage of subjects with photophobia freedom over time by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**Nausea freedom at all time points postdose**
Efficacy Endpoint	At each time point postdose, percentage of subjects with nausea absent at the time point for the subset with nausea present at the time of dosing
Summary	Percentage of subjects with nausea freedom over time by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use at or before time point: Composite strategy, i.e., intercurrent event captured in endpoint definition
Objective	**MQoL**
Outcomes Research Endpoint	Change from baseline in the total score at end of treatment visit
Summary	Mean change from baseline in total score by treatment group for the efficacy analysis set
Intercurrent Events	Rescue medication use: Treatment policy strategy, i.e., no accounting for intercurrent event
Objective	**PoM**
Outcomes Research Endpoint	Percentage of subjects who prefer study medication to previous migraine medications
Summary	Percentage of subjects in each category by treatment group for the efficacy analysis set with PoM data
Intercurrent Events	Rescue medication use: Treatment policy strategy, i.e., no accounting for intercurrent event
Objective	**Safety and tolerability**
Safety Endpoint	Frequency of adverse events (AEs) of at moderate or severe intensity, serious adverse events (SAEs), clinically relevant laboratory test abnormalities, and nasal inspection abnormalities
Summary	Number and percentage of subjects with safety events and findings for the safety analysis set
Intercurrent Events	Rescue medication use: Treatment policy strategy, i.e., no accounting for intercurrent event
Objective	**S-STS**
Safety Endpoint	Change from baseline in the total score at end of treatment visit
Summary	Percentage of subjects in each change from baseline category (< -1, -1, no change, 1, > 1) by treatment group for the safety analysis set with S-STS data
Intercurrent Events	Rescue medication use: Treatment policy strategy, i.e., no accounting for intercurrent event

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.
- Randomized: Subjects in the enrolled analysis set who receive a randomized treatment assignment from the IWRS, i.e., non-missing IWRS randomization date.
    - Efficacy: Subjects in the randomized analysis set who (1) are randomized only once, (2) have a migraine of moderate or severe pain intensity at the time of dosing, (3) take study drug, and (4) have postdose efficacy data (i.e., non-missing pain intensity, phonophobia status, photophobia status, nausea status, or functional disability level with finding date/time from the eDiary Postdose Migraine Report).
- Safety: Subjects in the enrolled analysis set who take study drug (zavegepant or placebo), i.e., non-missing study drug start date/time.
- Full: Subjects in the randomized 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.

4.2 Treatment Groups

The 2 treatment groups are zavegepant 10 mg and placebo. The safety analysis set is assessed by as-treated treatment group (i.e., actual treatment received), the randomized, full, efficacy, and outcomes research analysis sets are assessed by as-randomized treatment group, and the enrolled analysis set is assessed overall.

If a subject receives ≥ 1 dose of planned randomized study drug, then that subject is considered to have as-treated treatment group equal to as-randomized treatment group.

If there are non-randomized subjects who receive study drug, then the as-randomized treatment group of “not randomized” is included for the full analysis set.

4.3 Subgroups

For the efficacy analysis set, the following efficacy subgroups are of interest:

- Age: < 40, ≥ 40 years
- Sex: female, male
- Race: White, Black or African American, Other including Asian, Asian
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino

- Baseline body mass index (BMI; kg/m^2): < 25, ≥ 25 to < 30, ≥ 30
- Aura on study before dosing: yes, no (see Section 6.2.5.2)
- Historical number of moderate or severe migraine attacks per month: < median, ≥ median, where the median is calculated overall across treatment groups combined for the efficacy analysis set and rounded to an integer (see Section 6.2.5.2)
- Triptan non-responder: yes, no (refer to the Zavegepant Core SAP)

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

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

5 SAMPLE SIZE, POWER, AND TYPE 1 ERROR

It is anticipated that about 90% of the 700 subjects randomized to each treatment group will have a headache in the allotted time period, resulting in approximately 630 subjects evaluable for efficacy in each treatment group.

The sample size calculation is based on results from the Phase 2/3 dose-ranging study BHV3500-201. The response rates for the pooled zavegepant 10 mg and 20 mg groups, and for the placebo group in study BHV3500-201 were 22.8% and 15.5%, respectively, for pain freedom at 2 hours postdose, and 42.2% and 33.7%, respectively, for MBS freedom at 2 hours postdose.

A total sample size of 1,260 evaluable subjects (630 per treatment group) provides approximately 91% power for the co-primary endpoint of pain freedom at 2 hours postdose, approximately 88% power for the co-primary endpoint of MBS freedom at 2 hours postdose, and approximately 80% power to detect a difference between treatment groups for both endpoints jointly.

Type I error is controlled by a hierarchical gate-keeping procedure. First, the family of 2 co-primary endpoints is tested. In particular, zavegepant is tested for superiority against placebo at an alpha=0.05 level for both co-primary endpoints. If the tests of both co-primary endpoints are significant (i.e., both p-values are ≤ 0.05), then the secondary endpoints are tested hierarchically at the alpha=0.05 level in the order shown in the Section 3.1.2, using the efficacy analysis set. Thus, a secondary endpoint is tested only if the preceding secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

For exploratory endpoints, no attempt is made to adjust for multiplicity. Any exploratory endpoints for which p-values are produced are evaluated at an unadjusted, 2-sided alpha=0.05 level and presented only for descriptive purposes.

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.

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

6.1.1.1 Tables

Treatment Group Presentation

Tables present results by treatment group (i.e., zavegepant 10 mg and placebo) with the following exceptions:

- Results for the enrolled analysis set are presented only by overall, without treatment group.
- Results for study population parameters (see Section 6.2) and pre-treatment safety also include overall.

Time-to-event Tables

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

Time-to-event distributions of endpoints are tabulated with the following descriptive statistics: number and percentage of subjects with events; number and percentage of subjects censored in or before the last time interval; number and percentage of subjects censored in the last time interval; time-to-event median with 95% CI, first quartile, and third quartile. The 95% CI for the median is estimated using the method of Brookmeyer and Crowley.

6.1.1.2 Listings

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

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

Listings of non-study medications, safety 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.

Select listings 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

For all binary efficacy endpoints, main analyses impute missing data as failure using methods described in Section 6.3. Sensitivity analyses of the co-primary endpoints exclude subjects with missing data, or impute missing data using different methods (see Sections 6.3.2.1 and 6.3.2.2). Sensitivity analyses of exploratory efficacy endpoints exclude subjects with missing data (see Section 6.3.4.2). Otherwise, 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 by treatment group (as-randomized for the randomized, full, and efficacy analysis sets; as-treated for the safety analysis set), not randomized, and overall.

Inclusion and exclusion from the efficacy analysis set is tabulated by treatment group and overall as the number and percentage of subjects in the full analysis set in the following categories:

- Included in the efficacy analysis set
- Excluded from the efficacy analysis set
  - Treated with study drug (i.e., study drug start date/time not missing)
    - Not randomized
    - Randomized more than once
    - Pain intensity of mild, none, or not reported at the time of dosing
    - No postdose efficacy data (i.e., missing all of the following parameters from the eDiary Postdose Migraine Report after the study drug start date/time: pain intensity, nausea status, phonophobia status, photophobia status, and functional disability level)
  - Not treated with study drug.

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

A by-subject listing of subjects excluded from the efficacy analysis is provided for the full analysis set. The listing includes the reason(s) for exclusion (e.g., not treated with study drug), as described previously.

An administrative listing of randomization scheme and codes is provided for all randomization numbers and block numbers, even those not assigned to a subject. 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 randomization month and year is tabulated as the number and percentage of subjects in each time category defined by randomization month and year for the full analysis set. Study drug start month and year are used for non-randomized subjects who took study drug.

6.2.3 Subject Disposition

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

In tables, reasons for not completing a milestone are displayed in alphabetical order. The reason of "other" for not completing a milestone is displayed as "other" without the corresponding specify text.

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); reason for not completing the study, including specify text for "other" and AE preferred terms (PTs); IWRS randomization date; study drug start date/time; last contact date; and previous subject identifier from the Informed Consent/Demographic CRF. 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.

See Section 7.1 for derived dates.

6.2.3.1 Subject Disposition from Enrollment to Randomization

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

- Randomized
- Not randomized
  - Reasons for discontinuation (i.e., not completing the study), including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure are also included from the Inclusion/Exclusion Criteria CRF.
- Not randomized and terminated the study prematurely due to COVID-19 (see Section 9.1.4)
  - Reasons for premature termination, including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure are also be included from the Inclusion/Exclusion Criteria CRF.

6.2.3.2 Subject Disposition from Randomization to Treatment

Subject disposition from randomization to treatment is tabulated for the randomized analysis set by as-randomized treatment group and overall 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 discontinuation (i.e., not completing the study), 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 to End of Study

Subject disposition from treatment to end of study is tabulated for the safety analysis set by as-treated treatment group and overall as the number and percentage of subjects in the following categories:

- Completed the study (identified as those with "yes" response to the question "Did the subject complete the study?")
- Did not complete the study (identified as those with "no" response to the question "Did the subject complete the study?")
  - Reasons for not completing the study, including not reported
- Terminated the study prematurely due to COVID-19 (see Section 9.1.4)
  - Reasons for premature termination, including not reported.

Subject disposition is tabulated analogously for the efficacy analysis set by as-randomized treatment group and overall to support efficacy.

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.

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

Relevant protocol deviations are tabulated as the number and percentage of subjects in deviation categories by as-randomized treatment group and overall for the full analysis set. Results are shown by deviation type (eligibility, subject management), category, and subcategory in the order specified in Section 9.2. 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, current triptan response, and migraine characteristics at the time of dosing), (3) medical history, and (4) prior non-study medications. These are detailed in Sections 6.2.5.1 through 6.2.5.4, respectively.

Baseline characteristics are tabulated for each of the following analysis sets as follows:

- Efficacy analysis set: Baseline characteristics (1) through (4) by as-randomized treatment group and overall to support efficacy
- Safety analysis set: Baseline characteristics (1) through (4) by as-treated treatment group and overall to support safety

- Subjects in the enrolled analysis set but not in the full analysis set: Demographics and other relevant baseline characteristics, and migraine history by overall only
- Subjects in the full analysis set but not in the efficacy analysis set: Demographics and other relevant baseline characteristics, and migraine history by as-randomized treatment group and overall.

IWRS prophylactic migraine medication use at randomization (yes, no) is tabulated by as-randomized treatment group and overall for the randomized analysis set.

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

- Enrolled analysis set but not in the randomized analysis set: Last non-missing value
- Randomized analysis set but not in the safety analysis set: Last non-missing value at or before the IWRS randomization date
- Efficacy, safety, and outcomes research analysis sets: Last non-missing value in the pre-treatment analysis period; see Section 7.2).

"Last" is determined by the measurement date/time. Other criteria such as last entry date/time or laboratory test source 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, and 6.4.4.1 for handling of ties on the same measurement date or time.

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. Other relevant characteristics also include the following: IWRS prophylactic migraine medication use at randomization (yes, no); non-study stable prophylactic migraine medication use through randomization (yes, no; see Section 6.2.5.4).

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.

The migraine history table also displays the number of moderate to severe migraines per month categorized as < median and ≥ median, where the median is based on the efficacy analysis set (see Section 4.3).

Migraine Characteristics at the Time of Dosing

Migraine characteristics at the time of dosing include the following parameters:

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

An intensity of none for a symptom (nausea, photophobia, or phonophobia) is defined as a symptom status of absent. See Section 7.5.2 for additional details.

An overall 3 × 3 cross-tabulation of the historical MBS (i.e., from migraine history) as rows, and the MBS reported on study before dosing as columns is presented for the efficacy analysis set with non-missing paired MBS values. The number and percentage of subjects in the following row and column categories are tabulated: nausea, phonophobia, photophobia, marginal total. In addition, the following statistics are tabulated: asymmetric lambda value and 95% CI; symmetric lambda value and 95% CI; kappa coefficient value and 95% CI; and p-value from the chi-square test.

6.2.5.3 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 Non-study Medications

The following non-study medications are tabulated by therapeutic class and preferred name:

- Prior medications: all; prophylactic migraine
- Current medications: all; prophylactic migraine
- Stable prophylactic migraine medications through randomization.

Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See Section 6.2.6.2.

Stable medications through randomization are defined as those taken > 3 months before informed consent and through randomization, i.e., (1) informed consent date – imputed medication start date > 90 days, and (2) IWRS randomization date ≤ imputed medication stop date.

6.2.6 Exposure

6.2.6.1 Study Therapy

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

eDiary study drug exposure is tabulated by as-randomized treatment group and overall for the full analysis set that includes the number and percentage of subjects in the following categories:

- Study drug taken (i.e., study drug start date/time not missing)
  - Study drug taken before using eDiary (see Section 7.5.1.1)
  - Study drug actually received different from randomized treatment assignment (i.e., as-treated treatment group not equal to as-randomized treatment group).
- Study drug not taken (i.e., study drug start date/time missing).

Study drug accountability is tabulated by as-randomized treatment group and overall for the full analysis set, and includes the number and percentage of subjects in the following categories:

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

Two 2 × 3 cross-tabulations of eDiary study drug exposure and study drug accountability are provided for the full analysis set by overall treatment group only. The number and percentage of subjects in each category are tabulated follows:

- Categories for study drug exposure in rows are “study drug taken” and “study drug not taken”. Categories for study drug accountability in columns are “kit dispensed and returned”, “kit dispensed and not returned/return not reported”, and “kit not dispensed/dispense not reported”.

- Categories for study drug exposure in rows are “study drug taken” and “study drug not taken”. Categories for study drug accountability in columns are “IP used”, “IP not used”, and “IP use not reported”.

A by-subject listing of eDiary study drug exposure and study drug accountability is provided for the full analysis set containing the following:

- eDiary: study drug date/time. Only eDiary records with non-missing study drug date/time are displayed.
- Drug accountability: kit dispensed status (yes, no), kit returned status (yes, no), kit dispensed date, kit returned date, kit ID, IP used status (IP used, IP not used).

The listing identifies the following: invalid kit IDs; subjects who took study drug, had a kit dispensed, but did not return a kit or had kit return status missing as per first cross-tabulation; and subjects with discrepant data as per second cross-tabulation, i.e., (1) eDiary study drug date/time is non-missing but IP not used or not reported, or (2) eDiary study drug date/time is missing but IP used.

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

6.2.6.2 Concomitant Non-study Medications

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

- Concomitant medications: all; prophylactic migraine
- Rescue medications.

Concomitant and rescue medications are displayed in descending order of zavegepant 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.

Rescue medications are also tabulated by as-randomized treatment group for the efficacy analysis set to support efficacy.

A by-subject listing of non-study medications is provided by therapeutic class and preferred name for the enrolled analysis set. Medication types are identified. Prophylactic migraine and rescue medications are identified. Refer to the Zavegepant Core SAP for listing contents.

A by-subject listing of rescue medications is provided by therapeutic class and preferred name for the safety analysis set. The listing also displays the number of hours that rescue medication is taken from study drug.

Both listings display treatment day derived from the imputed start date and COVID-19 visit impact code for visits impacted by COVID-19 (see Section 9.1.5.2).

The following conventions apply to non-study medications:

- Non-study medications are identified from those reported on the Concomitant Medication and Rescue Medication CRFs. Note that the Concomitant Medication CRF 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.
- Concomitant medications are defined as those taken on or after study drug, i.e., (1) study drug start date ≤ imputed start or stop date, or (2) rescue medications.
- Rescue medications are defined as non-study medications reported on the Rescue Medication CRF with complete medication dates, and either (1) medication date/time after the study drug start date/time if the medication time and study drug start time are both not missing, or (2) medication date at or after study drug start date if the medication time or study drug start time is missing. Rescue medication dates are not imputed. Rescue medication times are not imputed, unless specified otherwise (see Section 6.3.4.3).

6.3 Efficacy

Efficacy analyses are based on the efficacy analysis set by as-randomized treatment group only (excluding overall).

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

All CIs are 2-sided. In treatment comparisons of binary endpoints, CIs are based on a normal approximation to the binomial distribution using asymptotic standard error (ASE). In descriptive analyses of binary endpoints, exact Clopper-Pearson CIs are used. Otherwise, CIs for continuous endpoints are based on the normal distribution.

Postdose efficacy data are slotted into analysis windows automatically by the eDiary (see Section 7.5.2). All efficacy endpoints are assessed using analysis windows, unless specified otherwise.

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

- Non-Completer = Failure (NC=F): Subjects with missing data at a single time point are classified as failures. This missing data imputation method is applied to endpoints based on data from a single time point (e.g., co-primary endpoints) as the main analysis method.
- Non-Completer with Missing Data at More than 1 Time Point = Failure (NC1=F): Subjects with missing data at > 1 time point postdose in a specified time period are classified as failures. This missing data imputation method is applied to endpoints that are based on data

from multiple time points (e.g., secondary endpoint of sustained pain freedom from 2 to 24 hours postdose) as the main analysis method.

- Non-Completer = Missing (NC=M): Subjects with missing data at a single time point are excluded from the analysis. This missing data exclusion method is applied to endpoints based on data from a single time point (e.g., co-primary endpoints) as a sensitivity analysis.
- Multiple imputation (see Section 6.3.2.1). This missing data exclusion method is applied only to the co-primary endpoints as a sensitivity analysis.
- Varying response rate imputation (see Section 6.3.2.1). This missing data exclusion method is applied only to the co-primary endpoints as a sensitivity analysis.

The intercurrent event of rescue medication use is handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication are classified as failures for all efficacy assessments that are reported at or after taking rescue medication, i.e., (1) rescue medication start date/time ≤ eDiary finding date/time if start time is not missing, or (2) rescue medication start date ≤ eDiary finding date if start time is missing; see Sections 6.2.6.2 and 7.1). This method applies to all efficacy analyses, except the secondary endpoint of rescue medication use within 24 hours postdose.

6.3.1 Overall Efficacy

A by-subject listing of eDiary migraine characteristics is provided for the randomized analysis set that displays parameters listed in Section 7.5.2 at the time of dosing and over time postdose. The rescue medication start date/time and time to rescue medication use in hours are also included (see Sections 6.3.3.8 and 7.1); data collected on or after the rescue medication start date/time are identified.

6.3.1.1 Overall Summary of Primary and Secondary Endpoints

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

- Response rate (i.e., “n/N” and percentage) and 95% CI for each treatment group
- Stratified percentage difference between treatment groups (zavegepant – placebo), 95% CI, and p-value.

Analyses are based on main methods described in Sections 6.3.2 and 6.3.3. Endpoints are displayed in the order presented in Sections 3.1.1 and 3.1.2. P-values that are determined to be significant based on the testing hierarchy are identified.

A forest plot of treatment comparisons of all primary and secondary endpoints tested hierarchically is produced for zavegepant versus placebo based on the overall summary. The plot displays the following statistics:

- Response rate (i.e., “n/N” and percentage) by treatment group

- Stratified percentage difference between treatment groups (zavegepant – placebo) and 95% CI.

Percentage differences with p-values that are determined to be significant based on the testing hierarchy are identified. Note that the plot displays results for *no* rescue medication use within 24 hours postdose and *no* pain relapse from 2 to 48 hours postdose so that positive percentage differences favor zavegepant for these secondary endpoints.

6.3.1.2 Missing Efficacy Data

Missing efficacy data are tabulated by treatment group as the number and percentage of subjects in the efficacy analysis set in the following categories:

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

In addition, missing pain intensity at 2 hours postdose are tabulated by subgroup level for each treatment group and overall for all subgroups specified in Section 4.3 plus the following subgroups:

- Pain intensity at the time of dosing (moderate or severe)
- MBS on study before dosing (nausea, phonophobia, or photophobia)
- Rescue medication use: yes, no.

6.3.2 Primary Efficacy Endpoints

Both co-primary efficacy endpoints are evaluated for the efficacy analysis set.

A by-subject listing of pain freedom and MBS freedom outcomes at each postdose time point is provided for the randomized analysis set that includes prophylactic migraine medication use at randomization, rescue medication start date/time (see Section 7.1), time to rescue medication start date/time in hours (see Section 6.3.3.8), pain intensity at the time of dosing, MBS on study before dosing, and reason for exclusion from the efficacy analysis set (see Section 6.2.1). See Section 6.3.4.1 for efficacy outcomes.

6.3.2.1 Pain Freedom at 2 Hours Postdose

Pain freedom at a single time point postdose is defined as having a pain intensity of none at that time point.

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

- Pain intensity of none at 2 hours postdose, i.e., in the 2-hour postdose analysis window
- No rescue medication taken at or before 2 hours postdose, i.e., (1) rescue medication start date/time missing, or (2) rescue medication start date/time > {eDiary finding date/time for the pain intensity assessment in the 2-hour postdose analysis window}.

Subjects who have any of the following are classified as failures:

- Rescue medication taken at or before 2-hours postdose (RM=F), i.e., (1) rescue medication start date/time ≤ {eDiary finding date/time for the pain intensity assessment in the 2-hour postdose analysis window}, or (2) (rescue medication start date/time – study drug start date/time) ≤ 135 minutes, the upper bound of the 2-hour postdose analysis window (see Section 7.3), if pain intensity is missing in the 2-hour postdose analysis window.
- Mild, moderate, or severe pain intensity at 2 hours postdose, i.e., in the 2-hour postdose analysis window
- Missing pain intensity at 2 hours postdose (NC=F), i.e., in the 2-hour postdose analysis window.

Main Analyses

Pain freedom outcomes at 2 hours postdose are tabulated by treatment group (see Section 6.3.4.1). Outcomes are tabulated analogously for each subgroup level of all efficacy subgroups of interest specified in Section 4.3.

The percentages of subjects with pain freedom at 2 hours postdose are compared between zavegepant and placebo using Cochran-Mantel-Haenszel (CMH) tests stratified by IWRS prophylactic migraine medication use at randomization (yes, no). In these analyses, the NC=F and RM=F methods are applied. The following statistics are presented:

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI by randomization stratum for each treatment group
- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group
- Percentage difference between treatment groups (zavegepant – placebo), ASE, 95% CI, and p-value by randomization stratum
- Stratified percentage difference between treatment groups (zavegepant – placebo), ASE, 95% CI, and p-value.

The stratified percentage difference between zavegepant and placebo is tested at an alpha level of 0.05. Zavegepant is considered to be superior to placebo for this co-primary endpoint if the p-value for the stratified percentage difference is < 0.05.

The main analysis is repeated unstratified for each subgroup level of all efficacy subgroups of interest specified in Section 4.3.

Sensitivity Analyses

Sensitivity analyses include the following:

- Complete cases: The main analysis is repeated using NC=M, i.e., subjects who have missing pain intensity in the 2-hour postdose analysis window are excluded. First, the RM=F method of handling rescue medication use is applied. Next, subjects with missing pain intensity in the 2-hour analysis window are excluded. The same statistics as the main analysis are tabulated.
- Multiple imputation: The main analysis is repeated using the copy from reference multiple imputation approach with m=20 imputations to impute missing pain intensity at 2 hours postdose. The fully conditional specification (FCS) method is used with a generalized logit distribution. Covariates may include prophylactic migraine medication use at randomization (yes or no), sex, pain intensity at the time of dosing (moderate or severe), historical number of moderate to severe migraine attacks per month (< median, ≥ median), and MBS on study before dosing (nausea, phonophobia, or photophobia). First, the RM=F method of handling rescue medication use is applied. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed for subjects who are not missing any of the covariates (subjects missing any of the covariates are considered failures). The same statistics as the main analysis are presented.
- Varying response rate imputation: The main analysis is repeated by imputing missing pain intensity at 2 hours postdose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, the RM=F method of handling rescue medication use is applied. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed. The following statistics are presented: stratified percentage difference between treatment groups (zavegepant – placebo), ASE, 95% CI, and p-value.

6.3.2.2 MBS Freedom at 2 Hours Postdose

MBS freedom at a single time point postdose is defined as the MBS reported on study before dosing that is absent at that time point, e.g., subjects who report nausea as the MBS on study before dosing and have nausea absent at 2 hours postdose. The MBS on study before dosing is reported as nausea, phonophobia, or photophobia. Symptom status is reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).

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

- MBS reported on study before dosing that is absent at 2 hours postdose, i.e., in the 2-hour postdose analysis window
- No rescue medication taken at or before the 2 hours postdose, i.e., (1) rescue medication start date/time missing or (2) rescue medication start date/time > {eDiary finding date/time for the MBS status assessment in the 2-hour postdose analysis window}.

Subjects who have any of the following are classified as failures:

- MBS missing on study before dosing (see Section 7.5.2)
- Rescue medication taken at or before 2 hours postdose (RM=F), i.e., (1) rescue medication start date/time ≤ {eDiary finding date/time for MBS status assessment in the 2-hour postdose analysis window}, or (2) (rescue medication start date/time – study drug start date/time) ≤ 135 minutes, the upper bound of the 2-hour postdose analysis window (see Section 7.3) if MBS status is missing in the 2-hour postdose analysis window
- MBS present at 2 hours postdose, e.g., nausea reported as MBS on study before dosing and nausea present in the 2-hour postdose analysis window
- MBS missing at 2 hours postdose (NC=F), e.g., nausea reported as MBS on study before dosing and nausea status missing in the 2-hour postdose analysis window.

Main Analyses

MBS freedom outcomes at 2 hours postdose are tabulated by treatment group (see Section 6.3.4.1). Outcomes are tabulated analogously for each subgroup level of all efficacy subgroups of interest specified in Section 4.3 plus MBS on study before dosing (nausea, phonophobia, photophobia).

The percentages of subjects with MBS freedom at 2 hours postdose are compared between zavegepant and placebo using CMH tests stratified by IWRS prophylactic migraine medication use at randomization (yes, no). In these analyses, the NC=F and RM=F methods are applied. The same statistics are tabulated as those for the main analysis of pain freedom at 2 hours postdose (see Section 6.3.2.1). The stratified percentage difference between each zavegepant treatment group and placebo is tested at an alpha level of 0.05. Zavegepant is considered to be superior to placebo for this co-primary endpoint if the p-value for the stratified percentage difference is < 0.05.

The main analysis is repeated unstratified for each subgroup level of all efficacy subgroups of interest specified in Section 4.3 plus MBS reported on study before dosing (nausea, phonophobia, photophobia).

Sensitivity Analyses

Sensitivity analyses include the following:

- Complete cases: The main analysis is repeated using NC=M, i.e., subjects who have missing MBS status in the 2-hour postdose analysis window are excluded. First, subjects whose MBS on study before dosing is missing are classified as failures. Next, the RM=F method of handling rescue medication use is applied. Finally, subjects with missing MBS status in the 2-hour postdose analysis window are excluded.
- Multiple imputation: The main analysis is repeated using the copy from reference multiple imputation approach with m=20 imputations to impute missing MBS status in the 2-hour postdose analysis window. First, subjects whose MBS on study before dosing is missing are

classified as failures. Next, the RM=F method of handling rescue medication use is applied. Finally, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed.

- Varying response rate imputation: The main analysis is repeated by imputing missing MBS at 2 hours postdose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, subjects whose MBS on study before dosing is missing are classified as failures. Next, the RM=F method of handling rescue medication use is applied. Finally, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed.

See Section 6.3.2.1 for additional details about methods and the presentation of statistics.

6.3.3 Secondary Efficacy Endpoints

All secondary efficacy endpoints are evaluated for the efficacy analysis set, unless specified otherwise.

If the co-primary endpoint tests are both significant for zavegepant versus placebo, then the secondary endpoints are tested for zavegepant versus placebo using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at alpha=0.05. The endpoints are tested in the order shown in Section 3.1.2.

A by-subject listing of outcomes for pain relief, return to normal function, phonophobia freedom, photophobia freedom, and nausea freedom is provided for the randomized analysis set at each time point postdose. The listing also includes IWRS prophylactic migraine medication use at randomization and time to rescue medication start date/time in minutes (see Section 6.3.3.8), as well as functional disability level, phonophobia status, photophobia status, and nausea status at the time of dosing. See Section 6.3.4.1 for efficacy outcomes over time.

6.3.3.1 Pain Relief at 15 Minutes, 30 Minutes, 60 Minutes, and 2 Hours Postdose

Pain relief at a single time point postdose is defined as a pain intensity of none or mild at that time point.

Pain relief outcomes at 2 hours postdose are tabulated by treatment group (see Section 6.3.4.1).

At each time point postdose (15 minutes, 30 minutes, 60 minutes, and 2 hours), treatment group comparisons of the percentage of subjects with pain relief use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.2.1).

6.3.3.2 Return to Normal Function at 15 Minutes, 30 Minutes, 60 Minutes, and 2 Hours Postdose

Return to normal function at a single time point postdose is defined as a functional disability level of normal at that time point for subjects with functional disability at the time of dosing. Functional disability is defined as a functional disability level of mildly impaired, severely

impaired, or requires bedrest. Thus, all analyses of return to normal function are based on the efficacy analysis set with functional disability at the time of dosing (see Section 7.5.2).

Return to normal function outcomes at 2 hours postdose are tabulated by treatment group (see Section 6.3.4.1).

At each time point postdose (15 minutes, 30 minutes, 60 minutes, and 2 hours), treatment group comparisons of the percentage of subjects with return to normal function use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.2.1).

6.3.3.3 Sustained Pain Relief From 2 to 24 Hours Postdose

Sustained pain relief from 2 to 24 hours postdose is defined as pain intensity of none or mild at all time points from 2 to 24 hours postdose.

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

- Pain intensity of none or mild at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before 24 hours postdose, i.e., (1) rescue medication start date/time missing or (2) rescue medication start date/time > {eDiary finding date/time for the pain intensity assessment in the 24-hour postdose analysis window}.

Subjects who have any of the following are classified as failures:

- Rescue medication taken at or before 24 hours postdose (RM=F), i.e., (1) rescue medication start date/time ≤ {eDiary finding date/time for the pain intensity assessment in the 24-hour postdose analysis window}, or (2) (rescue medication start date/time – study drug start date/time) ≤ 25 hours, the upper bound of the 24-hour postdose analysis window (see Section 7.3), if pain intensity is missing in the 24-hour postdose analysis window.
- Moderate or severe pain intensity at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8 or 24-hour postdose analysis window
- Missing pain intensity at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

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

- Responder: (1) Pain intensity of none or mild at all time points from 2 to 24 hours postdose, (2) missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, and (3) no rescue medication taken at or before 24 hours postdose
- Failure
    - Rescue medication taken at or before 24 hours postdose (RM=F)
    - Moderate or severe pain intensity at any time point from 2 to 24 hours postdose
        - Severe pain intensity
        - Moderate pain intensity
    - Missing pain intensity at 2 or 24 hours postdose (NC=F)
    - Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F).

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

Treatment group comparisons of the percentage of subjects with sustained pain relief from 2 to 24 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.2.1).

6.3.3.4 Sustained Pain Relief From 2 to 48 Hours Postdose

Sustained pain relief from 2 to 48 hours postdose is defined as pain intensity of none or mild at all time points from 2 to 48 hours postdose.

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

- Pain intensity of none or mild at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before 48 hours postdose, i.e., (1) rescue medication start date/time missing or (2) rescue medication start date/time > {eDiary finding date/time for the pain intensity assessment in the 48-hour postdose analysis window}.

Subjects who have any of the following are classified as failures:

- Rescue medication taken at or before 48 hours postdose (RM=F), i.e., (1) rescue medication start date/time ≤ {eDiary finding date/time for the pain intensity assessment in the 48-hour postdose analysis window}, or (2) (rescue medication start date/time – study drug start date/time) ≤ 49 hours, the upper bound of the 48-hour postdose analysis window (see Section 7.3), if pain intensity is missing in the 48-hour postdose analysis window.

- Moderate or severe pain intensity at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing pain intensity at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

Sustained pain relief from 2 to 48 hours outcomes are tabulated for the efficacy analysis set by treatment group as the number and percentage of subjects in the following categories:

- Responder: (1) Pain intensity of none or mild at all time points from 2 to 48 hours postdose, (2) missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, and (3) no rescue medication taken at or before 48 hours postdose
- Failure
    - Rescue medication taken at or before 48 hours postdose (RM=F)
    - Moderate or severe pain intensity at any time point from 2 to 48 hours postdose
        - Severe pain intensity
        - Moderate pain intensity
    - Missing pain intensity at 2, 24, or 48 hours postdose (NC=F)
    - Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F).

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

Treatment group comparisons of the percentage of subjects with sustained pain relief from 2 to 48 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.2.1).

6.3.3.5 Sustained Pain Freedom From 2 to 24 Hours Postdose

Sustained pain freedom from 2 to 24 hours postdose is defined as pain intensity of none at all time points from 2 to 24 hours postdose.

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

- Pain intensity of none at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before 24 hours postdose (see Section 6.3.3.3).

Subjects who have any of the following are classified as failures:

- Rescue medication taken at or before 24 hours postdose (RM=F; see Section 6.3.3.3)
- Mild, moderate, or severe pain intensity at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8 or 24-hour postdose analysis window
- Missing pain intensity at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

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

- Responder: (1) Pain intensity of none at all time points from 2 to 24 hours postdose, (2) missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, and (3) no rescue medication taken at or before 24 hours postdose
- Failure
    - Rescue medication taken at or before 24 hours postdose (RM=F)
    - Mild, moderate or severe pain intensity at any time point from 2 to 24 hours postdose
        - Severe pain intensity
        - Moderate pain intensity
        - Mild pain intensity
    - Missing pain intensity at 2 or 24 hours postdose (NC=F)
    - Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F).

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

Treatment group comparisons of the percentage of subjects with sustained pain freedom from 2 to 24 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.2.1).

6.3.3.6 Sustained Pain Freedom From 2 to 48 Hours Postdose

Sustained pain freedom from 2 to 48 hours postdose is defined as pain intensity of none at all time points from 2 to 48 hours postdose.

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

- Pain intensity of none at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows

- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before 48 hours postdose (see Section 6.3.3.4).

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

- Rescue medication taken at or before 48 hours postdose (RM=F; see Section 6.3.3.4)
- Mild, moderate or severe pain at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing pain intensity at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

Sustained pain freedom from 2 to 48 hours outcomes are tabulated for the efficacy analysis set by treatment group as the number and percentage of subjects in the following categories:

- Responder: (1) Pain intensity of none at all time points from 2 to 48 hours postdose, (2) missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, and (3) no rescue medication taken at or before 48 hours postdose
- Failure
    - Rescue medication taken at or before 48 hours postdose (RM=F)
    - Mild, moderate, or severe pain intensity at any time point from 2 to 48 hours postdose
        - Severe pain intensity
        - Moderate pain intensity
        - Mild pain intensity
    - Missing pain intensity at 2, 24, or 48 hours postdose (NC=F)
    - Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F).

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

Treatment group comparisons of the percentage of subjects with sustained pain freedom from 2 to 48 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F, NC1=F, and RM=F (see Section 6.3.2.1).

6.3.3.7 Freedom from Photophobia, Phonophobia or Nausea at 2 Hours Postdose

Freedom from each symptom (nausea, phonophobia, photophobia) at 2 hours postdose is assessed separately. Symptom status is measured as present or absent for each symptom (nausea, phonophobia, photophobia).

Symptom freedom at a single time point postdose is defined as a symptom absent at that time point for subjects with the symptom present at the time of dosing. Thus, all analyses of symptom freedom are based on the efficacy analysis set with the symptom present at the time of dosing (see Section 7.5.2), e.g., nausea freedom at a single time point postdose are based on subjects with nausea present at the time of dosing.

Symptom freedom outcomes at 2 hours postdose are tabulated by treatment group (see Section 6.3.4.1).

Treatment group comparisons of the percentage of subjects with symptom freedom at 2 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.2.1).

6.3.3.8 Rescue Medication Use within 24 Hours Postdose

Analyses are based on the evaluable efficacy analysis set, i.e., subjects in the efficacy analysis set with rescue medication start date on or before study drug start date + 1 day and missing rescue medication start time are excluded. Time to rescue medication use is measured from the study drug start date/time to the rescue medication start date/time.

No analysis window around the 24-hour postdose time point is used.

Rescue Medication Use within 24 Hours Postdose

Rescue medication use within 24 hours postdose is defined as time to rescue medication use ≤ 24 hours.

Treatment group comparisons of the percentage of subjects using rescue medication within 24 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom, except that the NC=F and RM=F methods are not applied because they are not applicable to this endpoint (see Section 6.3.2.1).

Time to Rescue Medication Use through 24 Hours Postdose

Time to rescue medication use through 24 hours postdose is assessed by treatment group as follows:

- Kaplan-Meier plot and table using 2-hour time intervals (i.e., 0 to 2, > 2 to 4, ... , > 24). The Kaplan-Meier plot displays the percentage of subjects taking rescue medication within 24 hours postdose on the y-axis versus time in hours on the x-axis.

- Time-to-event distribution table (hours), including a log-rank p-value (zavegepant versus placebo).

See Section 6.1.1.1 for time-to-event plot and table attributes. Rescue medication use through 24-hours postdose is considered as an event in these time-to-event analyses. Subjects who do not take rescue medication within 24 hours postdose are censored at 24 hours and 1 minute (i.e., 1441 minutes).

6.3.3.9 Pain Relapse from 2 to 48 Hours Postdose

Pain relapse from 2 to 48 hours postdose is defined as pain intensity of mild, moderate, or severe at any time point postdose after 2 hours postdose for subjects with pain intensity of none at 2 hours postdose. Thus, analyses of pain relapse are based on the efficacy analysis set with pain freedom at 2 hours postdose (see Section 6.3.2.1).

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

- Pain intensity of none at all time points after 2 hours postdose, i.e., in the 3 to 48-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point after 2 hours postdose, i.e., in the 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- No rescue medication taken at or before 48 hours postdose (see Section 6.3.3.4).

Subjects who have any of the following are classified as relapsers:

- Rescue medication taken at or before 48 hours postdose (RM=F; see Section 6.3.3.4)
- Mild, moderate, or severe pain intensity at any time point after 2 hours postdose, i.e., in the 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing pain intensity at > 1 time point after 2 hours postdose (NC1=F), i.e., in the 3, 4, 6, 8, 24, or 48-hour postdose analysis window.

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

- Non-relapser: (1) Pain intensity of none at all time points after 2 hours postdose, (2) missing pain intensity at ≤ 1 time point after 2 hours postdose, and (3) no rescue medication taken at or before 48 hours postdose
- Relapser
    - Rescue medication taken at or before 48 hours postdose (RM=F)
    - Mild, moderate, or severe pain intensity at any time point after 2 hours postdose
        - Severe pain intensity
        - Moderate pain intensity
        - Mild pain intensity

- Missing pain intensity at > 1 time point after 2 hours postdose (NC1=F).

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

Treatment group comparisons of the percentage of subjects with pain relapse from 2 to 48 hours postdose use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC1=F and RM=F (see Section 6.3.2.1).

6.3.4 Exploratory Efficacy Endpoints

All exploratory efficacy endpoints are evaluated for the efficacy analysis set, unless specified otherwise.

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

6.3.4.1 Efficacy Outcomes over Time: Main Analyses

Efficacy outcomes are tabulated for the efficacy analysis set by treatment group as the number and percentage of subjects in categories (responder; failure; failure subcategories) at each time point from 15 minutes through 48 hours postdose. Subjects who are not classified as responders at a time point are classified as failures. Failure subcategories are mutually exclusive, because subjects who meet more than 1 failure criterion are classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the specified hierarchy for an endpoint is chosen. Percentages for response rates are also shown with exact Clopper-Pearson 95% CIs.

Outcomes are presented separately for each of the following efficacy endpoints: pain freedom, MBS freedom, pain relief, nausea freedom, phonophobia freedom, photophobia freedom, and return to normal function. These analyses use the NC=F and RM=F methods to align with main analyses of co-primary and secondary endpoints (see Sections 6.3.2 and 6.3.3). Outcomes category nomenclature is as follows:

- “at time point” means in the analysis window of that postdose time point
- “No rescue medication taken at or before time point” means either (1) rescue medication start date/time missing, or (2) rescue medication start date/time > {eDiary finding date/time for the data assessment in the analysis window of that postdose time point}
- “Rescue medication taken at or before time point” means either (1) rescue medication start date/time ≤ {eDiary finding date/time for the data in the analysis window of that postdose time point}, or (2) (rescue medication start date/time – study drug start date/time) ≤ upper bound of the analysis window corresponding to that postdose time point (see Section 7.3), if the data are missing in the time point analysis window.

Outcomes for the efficacy analysis set are presented over time as described below. Subjects who are excluded from analyses have the following outcomes in by-subject listings:

- Subjects in the randomized analysis set who are not in the efficacy analysis set: "Not in the efficacy analysis set"
- Subjects in the efficacy analysis set with normal or missing functional disability level at the time of dosing for return to normal function: "Not evaluable: normal function at the time of dosing" or "Not evaluable: missing disability level at the time of dosing"
- Subjects in the efficacy analysis set with absent or missing symptom status at the time of dosing for photophobia freedom, photophobia freedom, and nausea freedom: "Not evaluable: symptom absent at the time of dosing" or "Not evaluable: symptom missing at the time of dosing".

Pain Freedom Outcomes over Time

Outcomes categories are defined as:

- Responder: Pain intensity of none at time point and no rescue medication taken at or before time point
- Failure
    - Rescue medication taken at or before time point (RM=F)
    - Mild, moderate, or severe pain intensity at time point
        - Severe pain intensity
        - Moderate pain intensity
        - Mild pain intensity
    - Missing pain intensity at time point (NC=F).

Pain Relief Outcomes over Time

Outcome categories are defined as:

- Responder: Pain intensity of none or mild at time point and no rescue medication taken at or before time point
- Failure
    - Rescue medication taken at or before time point (RM=F)
    - Moderate or severe pain intensity at time point
        - Severe pain intensity
        - Moderate pain intensity
    - Missing pain intensity at time point (NC=F).

MBS Freedom Outcomes over Time

Outcome categories are:

- Responder: MBS reported on study before dosing that is absent at time point, and no rescue medication taken at or before time point
- Failure
  - Missing MBS on study before dosing
  - Rescue medication taken at or before time point (RM=F)
  - Nausea reported as MBS on study before dosing and present at time point
  - Phonophobia reported as MBS on study before dosing and present at time point
  - Photophobia reported as MBS on study before dosing and present at time point
  - Missing MBS status at time point (NC=F).

Return to Normal Function Outcomes over Time

Analyses are based on the efficacy analysis set with functional disability at the time of dosing (see Section 7.5.2).

Outcomes categories are defined as:

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

Phonophobia Freedom, Photophobia Freedom, and Nausea Freedom Outcomes over Time

Freedom from each symptom (phonophobia, photophobia, and nausea) is evaluated separately. Analyses are based on the efficacy analysis set with the symptom present at the time of dosing (see Section 7.5.2).

Outcomes categories are defined as:

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

6.3.4.2 Complete Cases over Time: Sensitivity Analyses

Response rates corresponding to efficacy outcomes over time are also presented using complete cases for each of the following efficacy endpoints: pain freedom, pain relief, MBS freedom, return to normal function, phonophobia freedom, photophobia freedom, and nausea freedom. Percentages for response rates are also shown with exact Clopper-Pearson 95% CIs.

In these sensitivity analyses, subjects who are missing data in a postdose time point analysis window are excluded at that time point (NC=M). Results for the co-primary endpoints of pain freedom and MBS freedom at 2 hours postdose are the same as those for the complete cases sensitivity analyses (see Sections 6.3.2.1 and 6.3.2.2).

For MBS freedom, the following conventions are applied: (1) first, subjects whose MBS reported on study before dosing is missing are classified as failures; (2) next, the RM=F method of handling rescue medication use is applied; (3) finally, subjects with missing MBS status in the analysis window are excluded.

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

6.3.4.3 Time-to-event Efficacy Endpoints

The following time-to-event endpoints are analyzed:

- Pain freedom through 4 hours postdose
- Pain freedom through 8 hours postdose
- Pain relief through 4 hours postdose
- Pain relief through 8 hours postdose
- MBS freedom through 8 hours postdose for subjects with MBS reported on study before dosing
- Return to normal function through 8 hours postdose for subjects with functional disability at the time of dosing

- Phonophobia freedom through 8 hours postdose for subjects with phonophobia present at the time of dosing
- Photophobia freedom through 8 hours postdose for subjects with photophobia present at the time of dosing
- Nausea freedom through 8 hours postdose for subjects with nausea present at the time of dosing.

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

For a given time-to-event endpoint, subjects are considered to have an event through *X* hours (*X* = 4 or 8) if the first postdose eDiary finding date/time defining response is (1) at or before the upper bound of the *X*-hour analysis window in minutes (see Table 5), and (2) is before the imputed rescue medication start date/time, if not missing (see Section 7.1).

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

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

- Kaplan-Meier plot and table using the following time intervals postdose: 0 to 15, >15 to 30, > 30 to 45, > 45 to 60, > 60 to 90, > 90 to 120, > 120 to 180, > 180 to 240, > 240 to 360, > 360 to 495, and > 495 minutes. The Kaplan-Meier plot displays the percentage of subjects with the event on the y-axis versus time in minutes on the x-axis.
- Time-to-event distribution table (minutes), including a log-rank p-value (zavegepant versus placebo).

See Section 6.1.1.1 for additional table and plot attributes.

6.3.4.4 Efficacy Endpoints Compared over Time

Treatment group comparisons of the percentage of subjects achieving response over time use analogous methods as the main analysis of the co-primary endpoint of pain freedom with NC=F and RM=F (see Section 6.3.2.1) for the efficacy analysis set and the following endpoints:

- Pain freedom
- Pain relief
- MBS freedom
- Return to normal function for subjects with functional disability at the time of dosing
- Phonophobia freedom for subjects with phonophobia present at the time of dosing
- Photophobia freedom for subjects with photophobia present at the time of dosing

- Nausea freedom for subjects with nausea present at the time of dosing.

For each endpoint and time point from 15 minutes through 48 hours postdose, the following are presented:

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group
- Stratified percentage difference between treatment groups (zavegepant – placebo), ASE, 95% CI, and p-value.

Response at each time point is defined in Section 6.3.4.1. Note that some of these analyses overlap with those of primary and secondary efficacy endpoints in Sections 6.3.2 and 6.3.3.

6.4 Safety

Safety analyses are based on the safety analysis set by as-treated treatment group (i.e., the actual treatment received). Results for the overall treatment group are also presented in pre-treatment safety summaries.

Safety parameters include deaths, AEs, and the following findings: laboratory tests; vital signs; physical measurements; electrocardiograms (ECGs); procedures; and S-STS.

Analysis periods are pre-treatment and on-treatment (see Section 7.2). Refer to the Zavegepant Core SAP for slotting safety parameters into analysis periods.

Values and changes from baseline in safety findings (e.g., laboratory tests, vital signs and physical measurements, ECGs) and S-STS endpoints are tabulated as continuous variables descriptively at baseline and the end of treatment visit. These analyses are based on observed data without imputation and regardless of rescue medication use. In these tables of safety parameters excluding laboratory tests, if a subject has multiple values in the end of treatment analysis visit window (see Section 7.3), then the last non-missing value measured in the analysis period is used. 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 the end of treatment analysis visit window (see Section 6.4.2.3).

By-subject listings of safety parameters are described in subsections, and identify on-treatment data. In addition, a by-subject listing of procedures is provided for the enrolled analysis set. These listings display study day and treatment day derived from the measurement date relevant to the endpoint.

6.4.1 Adverse Events

AEs are displayed in tables and listings by SOC and PT, unless specified otherwise.

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

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; and AEs leading to study drug discontinuation for the safety analysis set. TEAEs are identified.

6.4.1.1 Deaths

Deaths are identified from any the following sources:

- AE CRF with any of the following: PT containing "death"; reported term containing "death"; outcome of fatal; "yes" response to the question "Did the AE result in death?"; non-missing death date.
- Study Exit Status CRF with early termination reason of death.

Deaths are tabulated by analysis period for the enrolled analysis set as follows: by treatment group for subjects treated with study drug (i.e., those in the safety analysis set); not treated with study drug; and overall. Counts are displayed without percentages.

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 of the following AEs: any AE; mild AE; moderate AE; severe AE; moderate or severe AE; AE related to study drug; SAE; SAE related to study drug; AE leading to study drug discontinuation; hepatic-related AE; potential drug abuse AE; cardiovascular AE; suicidality AE; and local irritation AE.

An AE overview is produced for each analysis period (pre-treatment, on-treatment) for the safety analysis set.

6.4.1.3 Pre-treatment AEs by SOC and PT

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

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

AEs are displayed in descending order of overall frequency within SOC and PT.

6.4.1.4 On-treatment AEs by SOC and PT

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

- AEs by intensity
- TEAEs by intensity
- AEs associated with study drug by intensity
- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs
- AEs leading to study drug discontinuation
- Hepatic-related AEs by intensity *
- Cardiovascular AEs *
- Suicidality AEs *
- Local irritation AEs by intensity *.

AEs of special interest are asterisked ("*"). AEs are displayed in descending order of zavegepant frequency within SOC and PT.

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.

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 (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.

- Liver function test (LFT) values and ratios to ULN (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL], and alkaline phosphatase [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.
- 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.

6.4.2.2 Liver Function Test Elevations

Refer to the Zavegepant Core SAP for additional details.

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

The number and percentage of subjects with LFT elevations are tabulated separately for each analysis period (pre-treatment, on-treatment) for the safety analysis set. LFT elevations are based on fold changes above ULN.

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.

eDISH Scatter Plot

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.

6.4.2.3 Laboratory Test Changes from Baseline

Values and changes from baseline in laboratory tests are tabulated as continuous variables at baseline and the end of treatment visit.

If a subject has multiple values in the end of treatment analysis visit window, then a single value is selected using the following hierarchy as available:

- Non-missing viable value collected last. 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 last. If there are multiple values on the same date, then the value with the last accession identifier is used.

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.

Physical measurements include height (collected 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 sign and physical measurement parameters are tabulated as continuous variables at baseline and the end of treatment visit.

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 categories specified in the Zavegepant Core SAP.

6.4.4 Electrocardiogram

ECG parameters include RR, QRS, PR, QT, QTcF, and ventricular heart rate, which are measured with both date and time by the external source CCI

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 parameters are tabulated as continuous variables at baseline and the end of treatment visit.

If there are multiple values on the same measurement date and time, then the value with the last ECG reference 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.

6.4.4.3 ECG Abnormalities

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

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 as continuous variables at baseline and the end of treatment visit. The number and percentage of subjects in each change from baseline category (i.e., < -1, -1, no change, 1, > 1) are also presented for the ideation subscale, behavior subscale, and total score.

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 Safety Narratives

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

- All deaths for the enrolled analysis set
- On-treatment SAEs for the safety analysis set treated with zavegepant
- All AEs leading to discontinuation of study drug for the safety analysis set treated with zavegepant

- On-treatment events of special interest for the safety analysis set treated with zavegepant:
  - ALT or AST > 3x ULN
  - ALT or AST > 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
  - Cardiovascular AEs
  - Suicidality AEs.

Refer to the Zavegepant Core SAP for additional details.

6.5 Outcomes Research

Outcomes research endpoints are exploratory, and are assessed by as-randomized treatment group at 24 hours postdose using the eDiary for the efficacy analysis set. Postdose data are slotted into the 24-hour postdose analysis window automatically by the eDiary (see Section 7.5.3).

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

Refer to the Zavegepant Core SAP for details about outcomes research rating scale and questionnaires.

6.5.1 MQoL

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

MQoL total, domain, and item scores are tabulated by as-randomized treatment group as (1) continuous variables, and (2) the number and percentage of subjects in the categories defined in the Zavegepant Core SAP.

A by-subject listing of MQoL is provided for the enrolled analysis set, and presents the total score, domain scores, and item 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 from much better to much worse. Refer to the Zavegepant Core SAP for the 5 categories and additional combined categories.

PoM are tabulated as the number and percentage of subjects in each preference category (including combined categories) by as-randomized treatment group. Percentages are presented with exact Clopper-Pearson 95%. Analyses are provided for the following: (1) overall; (2) by pain freedom outcome at 2 hours postdose (responder, failure) for subjects who are included in the complete cases sensitivity analysis of pain freedom at 2 hours postdose (see Section 6.3.2.1).

A by-subject listing of PoM is provided for the enrolled analysis set.

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 visits according to COVID-19 visit date (see Section 7.3).

6.6.1 COVID-19 Overall Impact

COVID-19 visit impact is tabulated by as-treated treatment group and overall for the safety analysis set. The number and percentage of subjects in the categories defined by COVID-19 visit impact type, visit impact characteristics, and visit impact relationship are tabulated (see Section 9.1.1). 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 by analysis visit (Screening, Randomization, End of Study) and as-treated treatment group for the safety analysis set. The number and percentage of subjects in the categories defined by COVID-19 visit impact type, COVID-19 visit impact relationship are presented for each 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. A subject is evaluable at an analysis visit if the study day corresponding to the last contact date is ≥ lower bound of the analysis visit window. For subjects who took study drug but were not randomized, the treatment day corresponding to the last contact date is used instead.

6.6.3 COVID-19 Impact Listings

A by-subject listing of COVID-19 impact codes by visit displays visits (i.e., Screening, Randomization, End of Study) in separate columns for the enrolled analysis set. Each column denotes an analysis visit 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 visit, COVID-19 visit date, study day derived from the COVID-19 visit date, treatment day derived from the COVID-19 visit date, visit impact status, visit type (scheduled or unscheduled), visit impact type, visit impact characteristics, visit impact relationship, and premature study termination (yes; no; not applicable, subject continuing).

7 CONVENTIONS

7.1 Derived Dates

Derived dates are defined as follows:

- Study drug start date/time: Earliest (1) study medication dose date and time from the eDiary Migraine Report, or (2) study medication intake date and time from the Study Medication Intake Report (see Section 7.5.1). This date is used to define analysis periods.
- Rescue medication start date/time: Earliest rescue medication date/time (see Section 6.2.6.2). Missing time is considered to be earlier than non-missing time on the same date.
- Imputed rescue medication start date/time: This is used only for time-to-event efficacy analyses in Section 6.3.4.3, and not for time to rescue medication use analyses in Section 6.3.3.8.
    - If the rescue medication start date and time are both not missing, then the imputed rescue medication start date/time is set to the rescue medication start date/time.
    - If the rescue medication start time is missing and the rescue medication start date is equal to the study drug start date, then the imputed rescue medication start date/time is set to the study drug start date/time.
    - Otherwise, if the rescue medication start time is missing and the rescue medication start date is equal to a postdose eDiary finding date with non-missing efficacy data, then the

imputed rescue medication start date/time is set to the first eDiary finding date/time corresponding to non-missing efficacy data.

- Otherwise, if the rescue medication start time is missing and rescue medication start date is equal to the study drug start date + 1 day, then the imputed rescue medication start date/time is set to the study drug start date/time + upper bound of the *X*-hour analysis window (see Table 5).

- 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 AE CRFs, 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; eDiary study drug start; informed consent; IWRS randomization; laboratory collection; nasal inspection; non-study medication start or stop; 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 date 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:

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

See Section 7.1 for derived date/times 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

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

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

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

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

Analysis visit windows for safety parameters are presented in Table 4.

Table 4: Analysis Visit Windows for Safety Parameters

Analysis Visit	Analysis-Specified Interval
Screening	• ≤ Study day -1 or {both study day and treatment day missing} • ≤ Treatment day -1 *
Randomization	Study day 1
End of treatment	• ≥ Study day 2 • ≥ Treatment day 1 *

* Applies only to subjects who took study drug but were not randomized

See Section 7.5.2 for efficacy analysis windows and Section 7.5.3 for outcomes research analysis windows.

7.4 Duplicate Subjects

Duplicate subjects are those who re-screened once in study BHV3500-301 (per protocol), and are assigned more than 1 subject identifier. These subjects are identified from the Informed Consent/Demographics CRF, which captures the previous subject identifier. The following conventions apply:

- The unique subject identifier is derived as per the latest version of Biohaven Dataset Guidelines.
- The raw datasets contain data from all BHV3500-301 subject identifiers, with the unique subject identifier populated across records.
- The analysis datasets contain data as follows:
    - If the subject is in the full analysis set, then only data from the subject identifier corresponding to randomization or treatment in study BHV3500-301 are included.
    - If the subject is not in the full analysis set, then only data from the subject identifier corresponding to the last enrollment in study BHV3500-301 are included.
    - The unique subject identifier and previous BHV3500-301 subject identifier are populated across records.
- By-subject listings display subject identifier, but not unique subject identifier.

7.5 eDiary Data

7.5.1 Study Medication

7.5.1.1 eDiary Migraine Report

If the subject answered "yes" to taking study medication mistakenly already before using the eDiary, then the eDiary Migraine Report collects study medication data based on when the subject reported taking study medication (today, yesterday, or other) as follows:

- Today: Study medication dose date is set to the finding date, and study medication dose time is collected
- Yesterday: Study medication dose date is set to the finding date – 1 day, and study medication dose time is collected
- Other: Only the study medication dose date is collected (time is missing).

The eDiary Migraine Report derives the study medication dose date and time from all available data.

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

7.5.1.2 eDiary Study Medication Intake Report

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

7.5.2 Migraine Characteristics

The following migraine characteristics are collected on study (i.e., on or after the randomization date) (1) before or at the time of dosing in the eDiary Migraine Report and (2) postdose from 15 minutes through 48 hours (e.g., 15, 30, 45, 60, and 90 minutes; 2, 3, 4, 6, 8, 24 and 48 hours) in the eDiary Postdose Migraine Report:

- Pain intensity (none, mild, moderate, severe)
- MBS (nausea, phonophobia, photophobia) before dosing in the eDiary Migraine Report only
- Nausea status (present, absent)
- Nausea intensity (mild, moderate, severe), if nausea status is present
- Phonophobia status (present, absent)
- Phonophobia intensity (mild, moderate, severe), if phonophobia status is present
- Photophobia status (present, absent)

- Photophobia intensity (mild, moderate, severe), if photophobia status is present
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura (yes, no) preceding or accompanying headache before dosing in the eDiary Migraine Report only.

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

In general, if subjects answered "no" to taking study medication mistakenly already, had current pain intensity of moderate or severe before dosing, and did not use other headache medications, then the eDiary Migraine Report collects current levels of all parameters on study before dosing and at scheduled postdose time points.

Otherwise, if subjects answered "yes" to taking study medication mistakenly already and provided the time of study medication taken, then the eDiary Migraine Report collects all parameters listed above (1) retrospectively at the time of dosing except MBS and aura, and (2) prospectively at scheduled postdose time points (as applicable based on study medication time).

For analyses, migraine characteristics collected in the eDiary Migraine Report are considered to be "at the time of dosing", except MBS and aura, which is considered to be "on study before dosing".

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

Table 5: eDiary Automated Efficacy Analysis Windows

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

7.5.3 MQoL and PoM

The eDiary collects MQoL and PoM data at 24 hours postdose using an analysis-specified interval of 23 to 29 hours and a target time of study medication start time + 24 hours.

8 CONTENT OF REPORTS

The final CSR is produced after the final data base lock, which occurs after last subject last visit. All TLFs described in this SAP are produced for the final CSR. No interim analyses are planned.

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, subject continuing) [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 termination are based on reasons for 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).

COVID-19 measurements are slotted into 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:

- Previously treated with study drug in another BHV3500 study. Defined as subjects who received ≥ 1 dose of study drug (e.g., zavegepant or placebo) in another BHV3500 study. These are identified from the protocol deviation CTMS file.
- Randomized or treated with study drug more than once and assigned > 1 subject identifier. These are identified from the protocol deviation CTMS file.
- 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 any as any of the following subcategories:
  - Basilar migraine or hemiplegic migraine
  - Active chronic pain syndrome
  - Other pain syndrome, psychiatric condition, dementia, or significant neurological disorder other than migraine

- Major depressive disorder with atypical antipsychotics taken through randomization, 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, medical history 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/1.73 m^2 through randomization *
  - BMI ≥ 35 kg/m^2 through randomization and consented to Protocol Version 3 or lower *
  - BMI ≥ 40 kg/m^2 through randomization and consented to Protocol Version 4 *
  - S-STS total score > 0 through randomization. For subjects who are not treated with study drug, any S-STS total score > 0 during the study is considered a deviation.

  "Through randomization" is defined as a finding date on or after the informed consent date and on or before the IWRS randomization date. For the subcategories marked with "*", all non-missing values through randomization must meet the deviation criteria in order to be considered a deviation.

Protocol version for consent is from the Informed Consent/Demographic CRF.

Relevant subject management protocol deviations include the following categories:

- Prophylactic migraine medication use at randomization discrepant between IWRS and CRF data, defined as any of the following subcategories:
  - IWRS randomization stratum of yes, but no stable prophylactic migraine medication taken through randomization
  - IWRS randomization stratum of no, but stable prophylactic migraine medication taken through randomization.

  See Section 6.2.5.4 for the definition of non-study stable medication through randomization.
- Prophylactic migraine medication started or stopped from 3 months before informed consent to randomization. Defined as informed consent date – 90 days ≤ imputed non-study medication start or stop date ≤ IWRS randomization date.
- Study drug dosing error, defined as any of the following subcategories:
  - Study drug taken but not randomized

  - Study drug actually received different from randomized treatment assignment (see Section 6.2.6.1)
  - Study drug taken before using eDiary (see Section 6.2.6.1)
  - Study drug taken with mild or missing pain intensity at the time of dosing.
- Prohibited non-study medication usage, defined as any of the following subcategories:
  - Barbiturate taken up to 14 days before randomization or afterward #
  - Butterbur root or extract taken up to 14 days before randomization or afterward
  - Calcitonin gene-related peptide (CGRP) receptor antagonist biologic taken up to 6 months (180 days) before informed consent or afterward #
  - CGRP receptor antagonist small molecule taken up to 14 days before informed consent or afterward #
  - Ergotamine taken on or after informed consent
  - Medication administered nasally up to 14 days before informed consent or afterward #. Route must be nasal.
  - Muscle relaxant (excluding baclofen) taken on or after informed consent #
  - Narcotic taken up to 2 days before randomization 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 start date – 14 ≤ imputed start or imputed stop date ≤ study drug start date, or (2) imputed start date ≤ study drug start date – 14 < study drug start date ≤ imputed stop date.
  - Select strong CYP3A4 inhibitors taken up to 14 days before study drug #.

  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*.
- Rescue medication usage error, defined as any of the following subcategories:
  - Rescue medication taken at or before 2 hours postdose (see Section 6.3.2.1) #
  - Non-approved rescue medication taken #
  - Paracetamol > 1000 mg taken on any 1 day. Paracetamol may be a single drug or a component in any combination drug.

For the medication subcategories marked with "#", preferred names are displayed alphabetically as additional subcategories.

The IWRS randomization date is the reference date for "randomization". If the IWRS randomization date is missing, then the study drug start date is used.

Refer to the Zavegepant Core SAP for additional details about prohibited non-study medications and approved rescue medications.

10 REFERENCES

Not applicable.