Protocol BHV3500-302 (C5301006)

A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Zavegepant in Migraine Prevention

Statistical Analysis Plan

Version 9

Date: 30-May-2024

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SIGNATURE PAGE

Protocol Title: BHV3500-302: A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Zavegepant in Migraine Prevention

Document Version: 9

Date: 30-May-2024

Author: PPD

Signature: _PPD__

Date: _____

Approval

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

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

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

PPD

Signature: _PPD

Date: _____

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASE	Asymptotic standard error
AST	Aspartate aminotransferase
BLQ	Below the limit of quantification
BMI	Body mass index
CGI-c	Clinical Global Impression - change
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	Double-blind
DBT	Double-blind treatment
ECG	Electrocardiogram
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
EOFU	End of follow-up
EOT	End of treatment
HDL	High-density lipoprotein
IWRS	Interactive web response system
LDL	Low-density lipoprotein
LFT	Liver function test
LLOQ	Lower limit of quantification
LSLV	Last subject last visit
LSM	Least-squares mean
MDRD	Modification of diet in renal disease
MIDAS	Migraine Disability Assessment
MSQoL	Migraine Specific Quality of Life
OP	Observation Phase
PoM	Preference of medication
PT	Preferred term

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Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SGC	Soft gelatin capsule
SI	Systeme Internationale
SOC	System organ class
SM	Satisfaction with medication
TBL	Total bilirubin
TLF	Table, listing, and figure
ULOQ	Upper limit of quantification
ULN	Upper limit of normal

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REVISION HISTORY

Version	Description of Change
1	Original version (08-Sep-2021) based on Protocol Version 4
2	Amended version (29-Sep-2021) based on Protocol Version 4 Section 2.1: Specified that subjects are randomized 2:2:1:1 to a treatment group and that randomization is stratified. Section 2.2: Specified that the IWRS randomizes subjects to a treatment group at the Baseline Visit and that randomization is stratified. Section 2.4: Specified that SAP Version 2 is based on Protocol Version 4. Section 6.2.3: Moved text about by-subject listings to Sections 6.2.3.1, 6.2.3.3, and 6.2.3.4. Section 6.2.3.6: Specified identification of treatment in previous studies. Added a listing of previous study participation. Section 6.5: Modified the handling of multiple questionnaires or rating scale values in analysis visit windows. Sections 6.5.1 and 6.5.2: Specified that results are based on completed questionnaires. Specified the handling of multiple questionnaires on the same assessment date. Sections 6.5.3, 6.5.4, and 6.5.5: Specified the handling of multiple questionnaires or rating scale values on the same assessment date or time. Section 6.6.2: Modified the definition of evaluable at an analysis visit during pretreatment or on-treatment. Section 7.1: Modified the derivation of the eDiary reference date and study drug end date. Section 7.4: Removed.
3	Amended version (05-Jan-2022) based on Protocol Version 5.0 General: Changed “non-missing” to “nonmissing”, “pre-treatment” to “pretreatment”, “on-treatment” to “on-DBT”, “efficacy analysis set” to “DBT efficacy analysis set”, “first week migraine analysis set” to “first month analysis set”, “follow-up analysis set” to “follow-up safety analysis set”, and “study drug” to “DB study drug”. Renumbered objectives and endpoints. Added the “zavegepant pooled” treatment group to select tables. Section 1.2: Modified the schedule of analyses to account for the addendum report. Section 2.1: Replaced Screening Phase with Observation Phase. Specified the Open-label Extension Phase and modified the timing of follow-up visits. Updated Figure 1 and added Figure 2. Section 2.2: Specified that the IWRS also dispenses study drug during visits in the OLE Phase. Section 2.3: Removed text about interim analyses. Specified that TLFs for the CSR and subsequent database locks are produced unblinded. Section 2.4: Specified that SAP Version 3 is based on Protocol Version 5. Section 3.1.2: Moved the 3 safety objectives to the end. Added “during the DBT and OLE Phases” to the end of the 3 safety objectives. Section 3.1.3: Added 2 new objectives #5 and #12. Added “during the DBT and OLE Phases” to the end of objectives #8, 9, 13, 14, and 15. Section 3.2: Specified the external source of the eDiary data. Section 3.2.2: Modified Table 2 to align with changes in Section 3.1.2. Section 3.2.3: Modified Table 3 to align with changes in Section 3.1.3. Section 4.1: Modified the definition of the migraine analysis set. Defined the first month migraine, first week treated migraine, DBT safety, OL zavegepant safety, DB or OL zavegepant safety, interim safety, and PK analysis sets.

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Version	Description of Change
	Section 4.2.: Specified OL zavegepant dose groups in the OLE Phase.
	Section 4.3.2.1: New section “On-DBT Safety Subgroups”. Moved existing text in Section 4.3.2 here.
	Section 4.3.2.2: New section “On-OL Zavegepant Safety Subgroups”.
	Section 4.3.2.3: New section “On-DB or OL Zavegepant Safety Subgroups”.
	Section 5: Changed “zavegepant study” to “rimegepant study” (typo). Specified that only secondary efficacy and outcomes research endpoints are tested hierarchically.
	Section 6.1.1.1: Added the table presentation of the OL zavegepant, DB or OL zavegepant, and interim safety analysis sets. Modified the table presentation of the follow-up safety analysis set. Added Table 4 “Treatment Group Presentation in Tables by Analysis Sets”. Defined “Zavegepant Pooled”.
	Section 6.1.1.2: Specified the treatment group abbreviation for subjects not in the randomized analysis set in listings. Added zavegepant study day to listings. Modified the abbreviated names of the analysis periods.
	Section 6.2.1: Changed “14” to “24” for the OP. Specified as-treated for all safety analysis sets.
	Sections 6.2.3.3 and 6.2.3.5: Modified categories based on the changes to the DB Subject Status CRF and addition of OLE Subject Status CRF.
	Section 6.2.3.4: New section “Subject Disposition during the OLE Phase” based on OLE Subject Status CRF.
	Section 6.2.5: Added tables and defined baseline for the OL zavegepant and DB or OL zavegepant safety analysis sets.
	Section 6.2.5.1: Added age and age category at reference baseline to tables for the OL zavegepant and DB or OL zavegepant safety analysis sets.
	Section 6.2.5.4: Renamed as “Non-study Prior Medications”.
	Section 6.2.6.1: Specified that OL zavegepant 100 or 200 mg is taken during the OLE Phase, and updated kit type identifiers. Defined valid DB and OL wallet IDs based on respective kit list files. Changed “study drug” to “DBT”. Moved current text under “DBT Exposure”. Added 2 subsections “OL Zavegepant Exposure” and “DB or OL Zavegepant Exposure”.
	Section 6.2.6.2: Changed “Treatment Compliance” to “DB Treatment Compliance”, “tablet” to “capsule” (typo), and “maxdate” to “DB maxdate”. Added new section “OL Zavegepant Treatment Compliance”. Removed “Last 28 days before DB study drug start” category.
	Section 6.2.6.3: Renamed as “Non-study Concomitant and Follow-up Medications”. Defined on-DBT, on-OL zavegepant, and on-DB or OL zavegepant concomitant medications. Added output for the OL zavegepant and DB or OL zavegepant safety analysis sets.
	Section 6.3: Changed “eDiary reference” to “eDiary efficacy” throughout.
	Section 6.3.1: Specified that pretreatment measurements that are not in the OP analysis period are labeled “PRETRT”, criterion (1) of the migraine analysis set definition aligns with protocol exclusion criterion 6c, and results are prorated only in the DBT Phase, not the OP. Modified the algorithm for calculating results in the OP.
	Section 6.3.1.1: Changed “14” to “24” for the OP.
	Section 6.3.2.3: Modified the section title.
	Section 6.3.3.1: Specified that results are prorated only in the DBT Phase, not the OP.
	Section 6.3.3.3: Modified the algorithm for calculating results in the OP and each week.
	Section 6.3.3.5: Specified that analyses are based on the first week treated migraine analysis set, and that results support exploratory objective #5.
	Section 6.3.4: Specified that results are tabulated by zavegepant treatment group.
	Section 6.4: Specified that treatment group is as-treated according to Section 6.1.1.1. Added the OL zavegepant, DB or OL zavegepant, and interim safety analysis sets. Modified the algorithm for measurement slotting.

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Version	Description of Change
	Section 6.4.1.1: Modified algorithm for identifying deaths. Added zavegepant study day to the listing. Section 6.4.1.2: Added tables for the OL zavegepant, DB or OL zavegepant, and interim safety analysis sets. Section 6.4.1.5: New section "On-OL Zavegepant AEs". Added tables for the OL zavegepant safety analysis set. Section 6.4.1.6: New section "On-DB or OL Zavegepant AEs". Added tables for the DB or OL zavegepant safety analysis set. Section 6.4.1.7: New section "Post-DBT Pre-OL Zavegepant AEs". Added tables for the interim safety analysis set. Section 6.4.2: Removed sentence about clinically significant laboratory abnormalities. Added output for the OL zavegepant, DB or OL zavegepant, and interim safety analysis sets. Sections 6.4.3 and 6.4.4: Added output for the OL zavegepant, DB or OL zavegepant, and interim safety analysis sets. Section 6.4.6: Modified events of interest. Sections 6.5.1 to 6.5.5: Added results at Weeks 24 and 64 to tables. Added tables for the OL zavegepant efficacy analysis set. Section 6.5.3: Specified that PoM is assessed for subjects with "yes" response to the lead question. Section 6.6.2: Modified the definition of evaluable subjects in the pretreatment analysis period. Specified which visits are tabulated. Section 6.6.3: Added zavegepant study day to the listing. Section 7.1: Modified the derivation of the eDiary reference date, study drug end, study drug last, last contact, OP start, and OP end dates. Added the derivation of the DB study drug start, DB study drug end, OL zavegepant start, OL zavegepant end, OL zavegepant last, DB or OL zavegepant start, DB or OL zavegepant end, and DB or OL zavegepant last dates. Changed "Study Drug Exposure" to "IP Dosing". Section 7.2: Changed "follow-up efficacy" to "post-DBT efficacy". Defined the pre-OL zavegepant, pre-DB or OL zavegepant, on-DBT safety, OL zavegepant safety, DB or OL zavegepant safety, and interim safety analysis periods. Section 7.3: Defined zavegepant study days. Specified how (1) study days and follow-up days are used to define analysis visit windows in safety analysis periods, and (2) display of zavegepant study days in select listings. Renumbered Table 4 as Table 5. Changed Week 12 target day from 84 to 85. Added study visits Week 14 though Week 64 to Table 5. Section 8: Specified the timing of the CSR database and final database locks and content of the reports. Section 9.1.4: Modified study premature termination derivations. Section 9.2: Changed "Demographics CRF" to "Demographics/Informed Consent CRF". Specified the full analysis set efficacy data issues during the OP. Added OL zavegepant dosing errors.
4	Amended version (02-Mar-2022) based on Protocol Version 5 Section 6.1.1.1: Modified treatment group labels for results by OL zavegepant dose and overall in Table 4. Sections 6.2.3.3 and 6.2.3.4: Modified the derivations of the on-going, completed phase, and did not complete phase categories. Section 6.2.5.4: Removed prior medications. Changed "3 months" to "12 weeks" and "90" to "84", Section 6.2.6.1: Modified the derivations of cumulative DB study drug exposure, cumulative OL zavegepant exposure, and cumulative DB or OL zavegepant exposure. Section 6.2.6.2: Modified the derivations of actual cumulative DB capsule count and actual cumulative OL zavegepant capsule count.

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Version	Description of Change
	Section 6.2.6.3: Modified the definitions of non-study concomitant medications to consider missing study drug last date. Defined prophylactic migraine and acute migraine medications. Section 6.4: Moved text about the procedures listing to Section 6.4.5. Section 6.4.5: New section "Procedures". Section 7.1: Modified the derivation of the DB study drug last date. Section 9.2: Changed "3 months" to "12 weeks", "90" to "84", and "receptor antagonist" to "antagonist".
5	Amended version (26-May-2022) based on Protocol Version 6 General: Changed "Zavegepant Core SAP" to "Core SAP". Removed references to former Section 9.1 ("COVID-19 Visit Impact") and its subsections, and instead referenced the Core SAP for COVID-19 visit impact. Modified language to use phrases like "table of <specified endpoint> is provided" instead of "<specified endpoint> is tabulated". Changed "stop date" to "end date". Corrected hyperlink errors. Section 1: Specified that this SAP references the Rimegepant/Zavegepant Core SAP. Section 2.4: Specified that SAP Version 5 is based on Protocol Version 6. Sections 3.1, 3.2, and 3.3: Changed "baseline" to "the OP" in efficacy objectives and endpoints as per Protocol Version 6. Section 3.1.3: Added new objective #16 as per Protocol Version 6. Section 3.2.3: Added new endpoint #16 to Table 3 as per Protocol Version 6. Section 4.1: Changed the definition of the migraine analysis set back to SAP Version 2 definition based on FDA feedback on BHV3000-404. Modified the definition of the first week treated migraine analysis set to include DB study drug dosing days. Section 6.1.1.1: Modified last column of Table 3 to display abbreviated treatment group. Section 6.2.1: Specified that the COVID-19 impacted analysis set is excluded from the table. Section 6.2.3: Added a footnote to subject disposition listings about the last contact date. Section 6.2.3.3: Modified definitions of "continued to the next phase" and "did continue to the next phase" categories. Section 6.2.3.5: Modified definition of "did not formally enter the Follow-up Phase" category. Section 6.2.3.6: Moved text from Section 9.1.4 here. Section 6.2.5: Removed baseline derivations and instead referenced the Core SAP. Specified that tables of baseline characteristics are produced for the full analysis set excluded from the migraine analysis set only if > 5 subjects are in this analysis set. Section 6.2.5.2: Removed migraine history parameters that are covered in the Core SAP. Section 6.2.6.2: Added a by-subject listing of treatment compliance. Modified the definitions of the following compliance categories: more than the required number of DB capsules per day taken on any 1 day; no DB study drug taken for ≥ 3 days (not necessarily consecutive) in any 1 week through Week 12; more than the required number of OL zavegepant capsules per day taken on any 1 day; no OL zavegepant taken for ≥ 3 days (not necessarily consecutive) in any 1 week after Week 12 through Week 64. Added category "DB study drug and OL zavegepant taken on same day". Section 6.2.6.3: Removed the definitions of DB, OL zavegepant, and DB or OL zavegepant concomitant medications, and instead referenced the Core SAP. Section 6.3.1: Changed the definitions of the following back to SAP Version 2.0 definition: migraine analysis set; number of migraine days per month in the OP. Section 6.3.1.1: Changed "24" to "14" for the OP. Section 6.3.1.2: Added a table of values and changes from the OP in the number of migraine days per month in the DBT Phase for the DBT efficacy analysis set. Removed scatter plots.

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Version	Description of Change
	Section 6.3.2.1: Specified that results across all subgroups are displayed together in the same CMH table.
	Section 6.3.2.3: Added the number of subjects with data as a summary statistic.
	Section 6.3.3.5: Modified the definition of the first week treated migraine analysis set to include DB study drug dosing days.
	Section 6.4: Removed the algorithm for handling multiple measurements in the same analysis visit window, and instead referenced the Core SAP.
	Section 6.4.1: Added references to the Core SAP for AE end date imputation, death date derivation, and TLF contents.
	Section 6.4.1.1: Modifies the definition of deaths.
	Sections 6.4.1.2, 6.4.1.3, and 6.4.2.2: Changed "DBT safety analysis set" to "safety analysis set".
	Sections 6.4.1.4, 6.4.15, and 6.4.1.6: Specified analysis period reference start and end dates for calculations of exposure-adjusted multiple occurrences of unique AEs.
	Section 6.4.2.2: Specified that tables of exposure-adjusted cumulative LFT elevations use the same analysis period reference start and end dates as corresponding exposure-adjusted AEs. Modified the definition of treated migraine days to include study drug dosing days.
	Sections 6.4.2.3 and 6.4.3.1: Added overall treatment group to the table of values and changes from baseline for the safety analysis set. Specified the time points at which results for zavegepant pooled, placebo pooled, and overall are displayed. Removed text about handling multiple values on the same date, and instead referenced the Core SAP for handling multiple values in an analysis visit window or on the same date, and deriving the EOT value in an on-treatment safety analysis period.
	Section 6.4.2.3: Specified that Cerba Research provides sample code (vial/tube identifier), whereas ACM Global Laboratories provide accession identifier.
	Section 6.4.4: Specified that (1) ECGs are analyzed using results from local tests reported on ECG CRFs and the external central vendor Bioclinica, and (2) the ECG CRF collects RR in sec, not msec.
	Section 6.4.4.1: Added overall treatment group to the table of values and changes from baseline for the safety analysis set. Specified the time points at which results for zavegepant pooled, placebo pooled, and overall are displayed. Modified text about handling multiple values on the same date. Referenced the Core SAP for handling multiple values in an analysis visit window and deriving the EOT value in an on-treatment safety analysis period.
	Section 6.5: Specified the slotting of measurements into analysis periods and analysis visits, and a confidence level of 97.5% is used for CIs. Removed text about handling multiple values on the same date. Added references to the Core SAP for handling multiple values in an analysis visit window or on the same date, and deriving the EOT value in an outcomes research analysis period.
	Sections 6.5.1 and 6.5.2: Added overall treatment group to the table of values and changes from baseline for the DBT efficacy analysis set. Specified the time points at which results for overall are displayed.
	Sections 6.5.3, 6.5.4, and 6.5.5: Added overall treatment group to the frequency table for the DBT efficacy analysis set. Specified the time points at which results for overall are displayed.
	Section 6.6: Removed subsections 6.6.1 though 6.6.3. Referenced the Core SAP.
	Section 7.1: Specified which derived dates are analysis period reference dates. Modified the derivation of the OP end date and last contact date.
	Section 7.2: Defined the 28-day OP analysis period. Removed the definitions of analysis periods for pretreatment characteristics, safety endpoints, and outcomes research endpoints, and instead referenced the Core SAP.
	Section 7.3: Removed the definitions of randomization day, study day, rimegepant study day, and follow-up day, and instead referenced the Core SAP. Modified contents of Table 5 and added 2 footnotes.

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Version	Description of Change
	Section 9.1: Removed. Section 9.2: Renumbered as 9.1. Specified using the 28-day OP analysis period for assessing efficacy data issues during the OP. Specified that narcotic is barbiturate or opioid. Removed deviation category for St. John's wort because it is covered under CYP3A4 and P-gp inducer categories. Sections 9.3 and 9.4: Renumbered respectively as 9.2 and 9.3. Section 9.4: New section "Study Drug Dosing Days".
6	Amended version (11-Aug-2022) based on Protocol Version 6 Section 2.4: Specified that SAP Version 6.0 is based on Protocol Version 6. Section 3.2.2: Modified the efficacy endpoint for objective #2 in Table 2. Section 3.2.3: Modified the efficacy endpoint for objectives #1, 6, and 7 in Table 3. Section 6.1.1.1: Modified the treatment group layout of OL zavegepant safety and follow-up safety analysis sets by treatment group/OL zavegepant dose and overall in Table 4. Section 6.3.1: Specified that results are prorated to account for missing migraine reports. Section 6.3.2.1: Removed longitudinal plots. Section 6.3.4: Modified data sources, contents of the plasma zavegepant concentration listing, and merging of CRF and external PK data. Section 6.4.2.1: Specified the main presentation only for shift tables.
7	Amended version (11-May-2023) based on Protocol Version 6 General: Removed "Biohaven Pharmaceuticals" throughout. Added "(C5301006)" next to BHV protocol number, and footer "Pfizer Confidential". Removed statements throughout about displaying COVID-19 visit impact code for visits impacted by COVID-19 in listings. Added ', normal distribution' throughout after 'Identity link function'. Replaced the randomized analysis set with the full analysis set. Signature page: Removed all references to "sponsor". Replaced PPD with PPD, and PPD with PPD, and removed PPD. Abbreviations: Added CYP3A4, eDiary, and GLM. Removed CK, TEAE, and US. Section 1.2: Changed "CSR" to "first", and specified that no interim analyses are planned (moved text from Section 8). Removed the last sentence. Section 2.3: Changed "CSR" to "first", and removed "and subsequent database locks". Section 2.4: Specified that SAP Version 7 is based on Protocol Version 6. Section 3.1: In Table 1, formatted text to bold for primary objective. Section 3.2: Specified treatment group comparisons for efficacy and outcomes research endpoints. In the "Intercurrent Events" section, specified (1) hypothetical or composite strategy for handling study drug discontinuation for efficacy objectives, (2) 7-day cutoff on study drug discontinuation for safety objectives, and (3) non-study prophylactic migraine medication use before the time point of interest defining the endpoint as an intercurrent event for all objectives. Changed "change" to "mean change" and "value" to "mean value" in the "Summary" rows for continuous endpoints in Tables 1 to 3. In the "Data Sources for Endpoints" section, removed the sentence "Deaths are determined from AE and subject disposition case report forms (CRFs).". Section 3.2.1: In the first sentence, replaced "attributes" with "estimand" and removed "for this study are" after "endpoint". Modified the "Summary" and "Intercurrent Events" rows in Table 1. Section 3.2.2: In Table 2, (1) modified "Summary" row for objectives #1 to 6, and (2) modified "Intercurrent Events" row for all objectives. Sections 3.2.3: In Table 3, (1) modified "Summary" row for objectives #1 to 7, 10, and 11, (2) modified "Intercurrent Events" row for all objectives, and (3) formatted text to bold in rows for "Objective 4 and "Objective 16".

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Version	Description of Change
	Section 4.1: Removed the previous definition of the full analysis set.
	Section 4.3: Specified that the efficacy subgroup of interest is stable prophylactic migraine medication use through randomization.
	Section 4.3.1: Removed this section because all efficacy subgroups were removed except for randomization stratum, which was moved up to Section 4.3.
	Section 4.3.2: Removed this section because all safety subgroups were removed.
	Section 5: Specified 2-side alpha levels.
	Section 6.1.1.1: Removed references to safety subgroups.
	Section 6.1.1.2: Removed significant protocol deviations. Replaced 'COVID-19 visit impact' with 'visits impacted by COVID-19'.
	Section 6.1.3: Modified second sentence to reference Section 6.3 for statistical methods for handling missing data in efficacy analyses.
	Section 6.2.1: Removed the frequency table of inclusion and exclusion from the migraine analysis set and the listing of subjects excluded from efficacy analyses. Specified that the administrative listing of randomization scheme and codes is provided for the full analysis set.
	Section 6.2.2: Removed the frequency tables of enrollment by age group and accrual by randomization month and year.
	Section 6.2.3: Added the by-subject listing of subject discontinuation for the enrolled analysis set, and specified its contents.
	Section 6.2.3.1: Removed the by-subject listing of eligibility with inclusion/exclusion criteria.
	Section 6.2.3.3: Removed the frequency table of subject disposition for the migraine analysis set. Removed the by-subject listing of DBT subject disposition.
	Section 6.2.3.4: Removed the by-subject listing of OLE subject disposition.
	Section 6.2.3.5: Removed the frequency table of subject disposition for the as-treated treatment group/OL zavegepant dose and overall. Removed the by-subject listing of follow-up subject disposition.
	Section 6.2.3.6: Added reference to Section 6.2.3.1.
	Section 6.2.3.7: Removed the by-subject listing of rescreen and previous study participation.
	Section 6.2.4: Moved text from Section 6.2.4.1 here.
	Sections 6.2.4.1 and 6.2.4.2: Removed.
	Section 6.2.5: Removed tables of baseline characteristics for select analysis sets. Replaced 'IWRS stable prophylactic migraine medication' with 'prior prophylactic migraine medication use'. Removed the by-subject listing of cardiac and other risk factors.
	Section 6.2.5.1: Replaced 'IWRS stable prophylactic migraine medication' with 'prior prophylactic migraine medication use'.
	Section 6.2.5.2: Removed "Age at chronic migraine onset (years)" and "Number of headache-free days per month in the 3 months prior to screening" because the Core SAP was updated with these parameters. Specified that the frequency table of cardiac and other risk factors is provided only for the DBT safety analysis set. Changed "efficacy endpoint" to "migraine-related even day" and "Efficacy parameter" to "parameter".
	Section 6.2.6.1: Modified the contents of the by-subject listing of study drug. Removed tables of DB study drug exposure by subgroups. Removed reference to subgroups and exposure table by subgroups.
	For the last time on DB or OL zavegepant milestone category, changed '18 months' to '15 months' (typo).

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Version	Description of Change
	Section 6.2.6.2: Specified the required number of capsules per day by OL zavegepant dose group in the calculation of OL zavegepant capsule count compliance. Changed "< 80%" to "≥ 80%" and removed the no study drug taken for ≥ 3 days in any week category in the treatment compliance tables. Changed "≤ 23" to "≥ 24" in the table of eDiary usage compliance. Section 6.2.6.3: Renamed section as "Non-study Concomitant Medications". Removed frequency tables of non-study DB or OL zavegepant concomitant and follow-up medications. Simplified the definition of migraine standard of care medications. Section 6.3: Replaced IWRS stable prophylactic migraine mediation through randomization with use of prior prophylactic migraine medication. Removed by-subject listings of exploratory migraine and headache days per month endpoints. Section 6.3.1: Removed the by-subject listing of eDiary headache report. Section 6.3.1.1: Modified the contents of the frequency table of missing efficacy data in the OP and DBT Phase. Section 6.3.1.2: Removed the table of values and changes from the OP in the number of migraine days per month in the DBT Phase for the DBT efficacy analysis set. Section 6.3.1.3: Removed "n (i.e., number of subjects with data)" from the GLMEM table. Removed the longitudinal plot of LSM change from OP in the number of moderate or severe migraine days per month versus month of the DBT Phase. Removed "subject as a random effect" from the GLMEM. Specified that Protocol Versions 1 to 6 erroneously specify to include subject as a random effect in the GLMEM. Specified the J2R and tipping point sensitivity analyses to be on the DBT efficacy analysis set instead of the migraine analysis set. Removed the supplementary analysis of the DBT efficacy analysis set and subgroup analyses of the migraine analysis set. Section 6.3.2.1: Removed the frequency table of descriptive analyses, histogram, and CMH table of ≥ 50% reduction of moderate or severe pain intensity by subgroups. Specified that percentages are calculated against the number of subjects in the migraine analysis set. Removed reference to Non-evaluable = Failure. Replaced 'a Cochran-Mantel-Haenszel (CMH) test stratified' with 'Mantel-Haenszel risk estimation with stratification' and replaced 'CMH table' with 'table'. Added a note that the protocols specified that the stratified CMH test would be used for treatment groups comparisons, but that the Mantel-Haenszel risk estimation is the more appropriate test to use given the estimand is based on a difference in percentages between treatment groups. Section 6.3.2.2: Removed "change from OP in" from the description of the dependent variable and "subject as a random effect" from the GLMEM. Removed "n (i.e., number of subjects with data)" from the GLMEM table. Section 6.3.2.3: Described the hierarchical testing strategy for secondary endpoints. In last 2 main bullets, replaced 'in the last month of the' with 'over the entire'. Section 6.3.3.1: Specified that the table of values and changes has the same format as the one described in Section 6.3.1.2. Sections 6.3.3.2, 6.3.3.4, and 6.3.3.5: Replaced 'a CMH test stratified' with 'Mantel-Haenszel risk estimation with stratification' and replaced 'CMH table' with 'table'. Section 6.3.3.2: Specified that the percentage of subjects with reduction in the number of headache days during the DBT Phase is defined and assessed analogously to the percentage of subjects with reduction in the number of migraine days during the DBT Phase. Removed the frequency table of descriptive analyses. Removed reference to Non-evaluable = Failure. Section 6.3.3.3: Modified the calculation of migraine days per week in the OP and each week of the on-DBT efficacy analysis period. Removed "subject as a random effect" from the GLMEM. Removed "n (i.e., number of subjects with data)" from the GLMEM table. Section 6.3.3.4: Specified that analyses of headache days per week are defined analogously to those for migraine days per week. Removed the frequency table of descriptive analyses. Specified that percentages are calculated against the number of subjects in the first month migraine analysis set.

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Version	Description of Change
	Section 6.3.3.5: Specified that percentages are calculated against the number of subjects in the first week treated migraine analysis set. Added percentage of efficacy endpoint days in the OP to the table.
	Section 6.3.3.6: Specified that the table of the number of acute migraine medication days per month in the DBT Phase has the same format as the one in Section 6.3.2.2. Removed "The corresponding CMH table has the same format.".
	Section 6.4: Removed tables during pretreatment for the enrolled analysis set by overall.
	Section 6.4.1: Specified the sorting order of AE tables, and that the by-subject listing of AEs for the enrolled analysis set includes all AEs (i.e., non-SAEs and SAEs). Removed by-subject listings of SAEs, AEs leading to study drug discontinuation, and AEs of special interest.
	Section 6.4.1.1: Removed the frequency table of deaths.
	Section 6.4.1.2: Removed AE overview frequency tables during pretreatment for the enrolled analysis set and by subgroups.
	Section 6.4.1.3: Removed AE frequency tables for the enrolled analysis set.
	Section 6.4.1.4: Removed frequency tables of AEs occurring with ≥ 5% frequency, TEAEs by intensity, TEAEs occurring with ≥ 2% frequency in any zavegepant treatment group and greater than placebo after rounding, exposure-adjusted multiple occurrences of unique SAEs, exposure-adjusted multiple occurrences of SAEs related to study drug, exposure-adjusted multiple occurrences of non-SAEs with ≥ 5% frequency, and by subgroups. Clarified that AE frequency is presented in descending order of Zavegepant pooled within SOC and PT.
	Section 6.4.1.5: Renumbered as Section 6.4.1.6. Removed AEs of special interest, exposure-adjusted multiple occurrences of unique AEs (all variations), and by subgroups.
	Section 6.4.1.6: Renumbered as Section 6.4.1.7. Specified that frequency tables of on-DB or OL zavegepant AEs are provided for the same endpoints as in section 6.4.1.4.
	Section 6.4.1.7: Renumbered as Section 6.4.1.5.
	Section 6.4.2: Specified that TLFs display results in SI units, if applicable. Removed by-subject listings of laboratory tests by laboratory test group and pregnancy tests. Removed creatine kinase elevation questionnaire listing.
	Section 6.4.2.1: Removed frequency tables of laboratory test low/normal/high shift from baseline to any abnormal value for all analysis periods, laboratory test toxicity grade shift from baseline to the worst toxicity grade on OL zavegepant, and by subgroups.
	Section 6.4.2.2: Removed frequency tables of LFT elevations during pretreatment for the enrolled analysis set, LFT ULN shifts from baseline to the worst LFT elevation on OL zavegepant, exposure-adjusted cumulative LFT elevations on OL zavegepant, and time to time to first LFT elevation on OL zavegepant. Removed eDISH plot on OL zavegepant. Replaced "treated migraine days" with "DB study drug and OL zavegepant dosing days" in the by-subject longitudinal LFT plot.
	Section 6.4.2.3: Replaced the table of values and changes from OL zavegepant baseline with the corresponding one from DB or OL zavegepant baseline.
	Section 6.4.3: Added BMI definition. Removed the by-subject listing of vital signs and physical measurements.
	Section 6.4.3.1: Replaced the table of values and changes from OL zavegepant baseline with the corresponding one from DB or OL zavegepant baseline.
	Section 6.4.3.2: Removed the frequency table on OL zavegepant.
	Section 6.4.4: Removed the by-subject listing of ECG results.
	Section 6.4.4.1: Replaced the table of values and changes from OL zavegepant baseline with the corresponding one from DB or OL zavegepant baseline.
	Section 6.4.4.2: Removed.
	Section 6.4.4.3: Renumbered as Section 6.4.4.2. Removed the frequency table on OL zavegepant.

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Version	Description of Change
	Section 6.4.5: Removed. Section 6.4.6: Renumbered as Section 6.4.5. Removed the frequency table on OL zavegepant and the by-subject listing of C-SSRS. Section 6.4.7: Renumbered as Section 6.4.6. Section 6.5: Removed reference to the OL zavegepant efficacy analysis set. Removed by-subject listings of PoM, SM and CGI-c. Specified the contents of the by-subject listing of MSQoL and MIDAS. Referred to the Core SAP for calculating scores, imputing missing data, and deriving categories. Section 6.5.1: Removed 2 sentences above "Descriptive Analyses" because these methods were added to the Core SAP. Added a frequency table of MSQoL domain score increase from baseline categories for the DBT efficacy analysis set. Specified that treatment group comparisons were on subjects with paired data. Changed "GLMEM" to "GLM". Removed the table of values and changes from OL zavegepant baseline in scores for the OL zavegepant efficacy analysis set. Section 6.5.2: Removed 2 sentences above "Descriptive Analyses" because these methods were added to the Core SAP. Changed "GLMEM" to "GLM". Section 6.5.3: Removed the frequency table of PoM for the OL zavegepant efficacy analysis set. Section 6.5.4: Removed the frequency table of SM for the OL zavegepant efficacy analysis set. Section 6.5.5: Removed the frequency table of CGI-c for the OL zavegepant efficacy analysis set. Section 6.6: Removed the by-subject listing of COVID-19 impact codes by visit. Renamed the by-subject listing of COVID-19 visit impact to visits impacted by COVID-19. Section 7.1: Added the death date. Section 7.2: Removed the on-OL zavegepant efficacy, post-DBT pre-OL zavegepant efficacy and follow-up efficacy analysis periods. Removed references to the eDiary headache report listing. Section 7.3: Replaced 'rimegepant' with 'zavegepant' (typo). Modified analysis visit windows for the Screening and Pre-randomization Visits in Table 5. Removed "Baseline #" row and corresponding footnote from Table 5. Specified how analysis visit windows are defined according to analysis period. Section 8: Specified the TLFs produced for the CSR and Addendum Report. Section 9.1: Modified deviation about major depressive disorder. Changed "P-gp" to "strong P-gp". Section 9.3.1: Added "cl diff" to the lsmeans statement. Section 9.3.2: Renamed section as "GLM". Added "cl diff" to the lsmeans statement.
8	Amended version (27-Feb-2024) based on Protocol Version 6 Abbreviations: Removed FCS, GLM, GLMEM, J2R, MAR, MCMC, and MNAR. Added LSLV. General: Replaced 'GLMEM' with 'linear mixed effects model' and 'GLM' with 'linear regression model' throughout. Used 'model' or 'models' in place of 'GLMEM' or 'GLM' to avoid redundant text on the type of model. Section 1: Specified that the study was terminated prematurely for business reasons and not a safety concern, and the SAP was being amended to reduce the number of TLFs. Section 1.2: Revised study plans to have 1 final database lock after the last subject completes the follow-up week 8 visit and a final CSR. Section 2.3: Removed reference to an addendum report. Specified that dummy treatment groups are used for the draft TLFs for the final CSR prior to DBL, and TLFs for the final CSR are produced unblinded. Section 2.4: Specified that SAP Version 8 is based on Protocol Version 6. Section 3.2: In the data sources for endpoints sub-section, updated acute migraine medication days definition. Removed PoM, SM and CGI-c categories.

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Version	Description of Change
	Section 3.2.3: Specified that Table 3 only includes the endpoints to be assessed. In Table 3, updated sections for exploratory objectives: 1, 2, 6, 7, 10-12, and removed sections for exploratory objectives 3-5 and 13-16.
	Section 4.1: Removed text on headache days for migraine analysis set. Removed first month migraine, PK, and OL zavegepant efficacy analysis sets.
	Section 4.3: Specified that the randomization strata are based on the actual data and not those assigned in IWRS.
	Section 5: Removed language about Type 1 error, testing hierarchy for the primary and secondary endpoints, and exploratory endpoints. Stated that type 1 error is not applicable, and significance of the primary and secondary endpoints will not be evaluated.
	Section 6.1.1.1: In Table 4, removed OL zavegepant efficacy and PK by zavegepant treatment group.
	Section 6.1.1.2: Added listing of significant protocol deviations.
	Section 6.2.1: Removed by-subject listing of subjects excluded from the efficacy analysis.
	Section 6.2.3.3: Replaced 'CSR' with 'LSLV'.
	Section 6.2.3.4: Replaced 'final' with 'LSLV'. Removed subject disposition table for as-treated treatment group/OL zavegepant dose and overall.
	Section 6.2.3.7: Removed Section (treatment in previous studies).
	Section 6.2.4: Moved Relevant Protocol Deviations section to new Section 6.2.4.1.
	Section 6.2.4.1: Changed analysis set to full in by-subject listing of relevant protocol deviations.
	Section 6.2.4.2: Added new section for Significant Protocol Deviations.
	Section 6.2.5: Removed text for DB or OL zavegepant safety analysis set. Revised frequency table of randomization stratum to a frequency cross table of randomization stratum from IWRS vs actual data for the full analysis set by treatment group and overall.
	Section 6.2.5.1: Updated 2nd bullet to use randomization stratum based on actual data. Removed text for DB or OL zavegepant safety analysis set.
	Section 6.2.5.2: Removed table of migraine-related event days per week from OP for first migraine analysis set. Removed sentence on the percentage calculation. Removed reference to sections on headache days per month, migraine days per week and headache days per week.
	Section 6.2.5.4: Replaced 'standard of care' with 'acute'.
	Section 6.2.6.1: Removed administrative listing of investigational produce batch numbers.
	Section 6.2.6.2: Removed DB treatment compliance, OL zavegepant treatment compliance, and ediary usage compliance tables and by-subject listing of treatment compliance. Specified that DB treatment compliance, OL zavegepant treatment compliance, and ediary usage compliance categories are defined for relevant protocol deviations. In sub-sections for DB treatment compliance and OL zavegepant treatment compliance, changed '≥ 80' to '< 80'.
	Section 6.2.6.3: Removed bullet on migraine standard of care medications. Replaced 'standard of care' with 'acute'.
	Section 6.3: Specified that the randomization stratum used in analyses is based on actual data, not from IWRS, and provided the rationale. For the listing of primary and key secondary efficacy endpoints, specified the reasons for exclusion from the migraine analysis set and data methods for presenting endpoints. Removed p-values for all models.
	Section 6.3.1: Removed text about data from previous visit to current visit.

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Version	Description of Change
	Section 6.3.1.3: Removed 'Identity link function, normal distribution'. Removed "subject as a random effect' from the model. Changed 'Repeated measures error structure' to 'Covariance structure for repeated measures accounting for within-subject correlated errors' and modified text describing specification of the covariance structure. Changed 'degrees of freedom method: Kenward-Roger' to Standard error (SE) estimation method: Huber-White "sandwich" (refer to the Core SAP)". Removed the longitudinal plot. Removed sensitivity analyses: jump to reference and tipping point. Section 6.3.2.1: Replaced 'efficacy dates' with 'efficacy data dates'. In treatment group sub-section, removed ≥ 75% and 100% percentage reductions. Section 6.3.2.2: Removed text about data from previous visit to current visit. Specified that acute migraine medication days are prorated. Replaced 'reference time point' with 'efficacy data'. Removed 'Identity link function, normal distribution'. Changed 'Denominator degrees of freedom method: Kenward-Roger' to 'Standard error (SE) estimation method: Huber-White "sandwich" (refer to the Core SAP)'. Section 6.3.2.3: Removed text about p-values and hierarchical testing. Section 6.3.3: Removed Sections 6.3.3.1, 6.3.3.2, 6.3.3.3, 6.3.3.4 and 6.3.3.5. Section 6.3.3.6: Renumbered to Section 6.3.3.1. Section 6.3.3.1: Replaced 'reference time point' with 'efficacy data'. Section 6.3.4: Removed table of plasma zavegepant concentrations along with the text to support this table. Specified that the by-subject plasma zavegepant concentrations will be presented for the DBT efficacy analysis set. Section 6.4: For On-OL zavegepant for the OL zavegepant safety analysis set, specified to present by OL zavegepant dose and overall. Removed the following: 'OL zavegepant dose and overall, i.e., main presentation', 'Treatment group/OL zavegepant dose and overall, i.e., supplemental presentation'. Removed 'Both presentations are produced'. Section 6.4.1: Removed 'exposure-adjusted multiple occurrences of unique AEs'. Section 6.4.1.2: For the AE overview frequency table, removed rows for 'Mild AEs' and 'Moderate AEs', and changed row for 'Severe AEs' to 'Moderate or Severe AEs'. Section 6.4.1.4: Removed table for exposure-adjusted multiple occurrences of unique AEs along with the calculations. Section 6.4.1.5: Removed section. Section 6.4.1.6: Renumbered to Section 6.4.1.5. New Section 6.4.1.5: Specified to produce the same tables as in Section 6.4.1.4. Section 6.4.1.7: Removed section. Section 6.4.1.8: Renumbered to Section 6.4.1.6. Section 6.4.1.9: Removed section. Section 6.4.2.1: Removed 'Post-DBT pre-OL zavegepant for the interim safety analysis set' and 'On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set'. Removed tables of laboratory test grade shifts from baseline. Section 6.4.2.2: Removed bullet: Post-DBT pre-OL zavegepant for the interim safety analysis set. Removed LFT ULN shifts from baseline to worst elevation, exposure-adjusted cumulative LFT elevations, and time to first LFT elevation. Removed LFT plots. Sections 6.4.2.3 and 6.4.3.1: Removed table of values and changes from DB or OL zavegepant baseline. Sections 6.4.3.2 and 6.4.4.2: Updated from: ' On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set using DB or OL zavegepant baseline' to: On-OL zavegepant for the OL zavegepant safety analysis set using OL zavegepant baseline'. Section 6.4.4.1: Removed table of values and changes from DB or OL zavegepant baseline.

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Version	Description of Change
	Section 6.4.5: Updated from:' On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set' to: On-OL zavegepant for the OL zavegepant safety analysis set'. Section 6.4.6: Removed bullet: 'Pre-DB or OL zavegepant for the enrolled analysis set treated previously with zavegepant in studies BHV3500-201/301' Section 6.5: Removed redundant word 'efficacy'. Specified that the randomization stratum used in analyses is based on actual data. Removed the following outcomes research questionnaires and rating scales: PoM, SM, and CGI-c. Removed text about deriving EOT value. Removed p-values for all models. Section 6.5.1: Removed EOT. Under treatment group comparisons, specified to analyze restrictive role function only. Removed 'Identity link function, normal distribution'. Replaced 'Denominator degrees of freedom method: Kenward-Roger' with 'SE estimation method: See Section 6.3.1.3'. Removed reference to exploratory objective #10. Section 6.5.2: Specified to analyze total score only. Removed reference to exploratory objective #11. Sections 6.5.3, 6.5.4, and 6.5.5: Removed sections. Section 6.6: Specified that only the frequency table of overall COVID-19 impact will be produced. Removed tables for COVID-19 visit impact by visit and missing LFT data impacted by COVID-19 by visit. Section 7: Replaced 'reference' with 'measurement'. Replaced 'efficacy date' with 'efficacy data date'. Section 7.2: Removed headache days. Replaced 'efficacy date' with 'efficacy data date'. Removed PoM, SM, and CGI-c. Section 7.3: Modified analysis visit windows for the Screening and Pre-randomization Visits in Table 5. Section 8: Specified that all TLFs described in the SAP are produced for the LSLV final CSR. Section 9.1: Changed 'more than once and assigned' to under. Removed 'for the full analysis set'. Specified how to determine the protocol version to which subjects originally consented. In the medical history section, added 'present at screening'. Added: 'Active medical history status is also identified by the sponsor medical lead or designee from reviewing by-subject listings of medical history and AEs'. Included the definition of 'Present at screening'. Updated text on randomization stratum discrepancies between IWRS and the actual data. Additional checks added under OL zavegepant dosing issues. Section 9.2.3: Updated definition of acute migraine medication day. Sections 9.3.1 and 9.3.2: Modified the SAS code by adding the 'empirical' option and removing '/ ddfm=kenwardroger'.
9	Amended version (30-May-2024) based on Protocol Version 6 Signature page: Updated department name for author and approver. Abbreviations: Removed COVID-19, CYP3A4 and P-gp. Section 2.4: Specified that SAP Version 9 is based on Protocol Version 6. Section 3.2: In the intercurrent events subsection, added language for nonstudy acute migraine-specific medication use and nonstudy other medication use to treat headache or aura. Sections 3.2.1, 3.2.2 and 3.2.3: Added nonstudy acute migraine-specific medication use and nonstudy other medication use to treat headache or aura as intercurrent events for the primary objective, all secondary objectives, and exploratory objectives 1-2 and 6-12. Sections 3.2.2 and 3.2.3: In summary row for secondary objectives 7-9 and exploratory objectives 8-9, removed "and DB or OL zavegepant".

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Version	Description of Change
	Section 4.1: Removed "study population" in bullet for the DB or OL zavegepant safety analysis set. Removed the COVID-19 impacted analysis dataset.
	Section 6.1.1.1: In table 4, removed row for "OL zavegepant safety, follow-up safety by treatment group/OL zavegepant dose and overall". Removed 'and pretreatment safety' in last sentence.
	Section 6.1.1.2: Removed "All listings except administrative listings identify subjects who are impacted by COVID-19." and "and visits impacted by COVID-19 visit impact".
	Section 6.2.1: Removed "(excluding COVID-19 impacted)".
	Sections 6.2.3 and 6.2.3.1-6.2.3.5: Removed all bullets/categories relating to COVID-19.
	Section 6.2.3.4: Moved text for "by OL zavegepant dose and overall" from end of section to first sentence.
	Section 6.2.3.5: Moved text for "by as-treated treatment group/OL zavegepant status and overall" from end of section to first sentence.
	Section 6.2.3.6: Removed section.
	Section 6.2.5: Revised bullet for demographics and other relevant baseline characteristics for the OL zavegepant safety analysis set to use the baseline value (at randomization) and to present by OL zavegepant dose and overall. Removed ", and in COVID-19 analyses by analysis visit (see Section 6.6)."
	Section 6.2.5.1: Removed "and calculating age at a reference date" in first sentence. Added "categorical variables" at end of second sentence. Removed last two sentences on OL zavegepant baseline.
	Section 6.2.5.2: Corrected typo by replacing small circle with '≥' for the migraine days per month by pain intensity categories. Removed headache days per month by pain intensity. Specified that categories may be redefined or combined based on the availability of the data.
	Section 6.2.6.2: In second bullet of the DBT treatment compliance subsection, added "/OL zavegepant start" after "DB study drug end". In OLE treatment compliance subsection, revised first sentence of the second to last bullet to: "OL zavegepant start date before DB study drug end date." In the eDiary usage compliance subsection, added "/OL zavegepant start" after "DB study drug end".
	Section 6.2.6.3: Updated definition of acute migraine medications.
	Section 6.4: Removed "Pretreatment for the DBT safety analysis set by treatment group, zavegepant pooled, placebo pooled, and overall".
	Section 6.4.1: In Section 6.4.1.2 (AE overviews), for overview tables removed "Moderate or Severe" row, added "SAEs related to Study Drug" row, and removed "Pretreatment for the safety analysis set". Removed Section 6.4.1.3 (Pretreatment AEs) and renumbered other subsections accordingly. Changed "by intensity" to "by worst intensity" in subsections. In new Section 6.4.1.3 (on DBT AEs), removed bullet "AEs of special interest" and sub-bullet "Medication-overuse headache AEs", and removed "by relationship to study drug (related, possibly related, unlikely related, not related, not reported)" from AE related to study drug table.
	Section 6.4.2.2: Removed "Pretreatment for the safety analysis set".
	Sections 6.4.3.2 and 6.4.4.2: Removed "using OL zavegepant baseline".
	Section 6.4.6: Updated criteria to identify participants with non-SAEs leading to discontinuation, select hepatic-related non-SAEs, cardiovascular non-SAEs, and suicidality non-SAEs.
	Section 6.6: Removed section.
	Section 7.1: Modified the definition of the last contact date to exclude the COVID-19 visit date.
	Section 7.2: Removed "and to assess pretreatment safety endpoints". Removed the pre-OL zavegepant and pre-DB or OL zavegepant safety analysis periods. Modified the purpose of the on-treatment safety analysis period.

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Version	Description of Change
	Section 7.3: Removed “on-DB or OL zavegepant and” from first sentence after table 5. Removed “Zavegepant study days are used to define analysis visit windows in the on-DB or OL zavegepant safety analysis period.” and “Analysis visit windows in the on-DB or OL zavegepant safety analysis period are defined analogously to those in the on-treatment safety analysis period.”.
	Section 9.1: Replaced “taken during the DBT Phase” with “start before DB study drug end”. Added “/OL zavegepant start” after “DB study drug end”. For prohibited non-study medications, removed CYP3A4 and P-gp inducer and inhibitors.

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1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

This document presents the statistical analysis plan (SAP) for Protocol BHV3500-302 (C5301006): A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Zavegepant in Migraine Prevention.

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

This SAP also references the Rimegepant/Zavegepant Core SAP, which is hereafter referred to as the "Core SAP".

Note that the study was terminated prematurely in December 2023 for business reasons and not a safety concern. As a result, the SAP is being amended from Version 7 to 8 to reduce the number of TLFs for the CSR in order to focus only on the most relevant objectives.

1.1 Research Hypothesis

Zavegepant 100 mg or zavegepant 200 mg soft gelatin capsule (SGC) oral dose taken daily is safe and effective for the prevention of migraine.

1.2 Schedule of Analyses

There is 1 planned database lock, last subject last visit (LSLV) database lock, which occurs when the last subject completes the Follow-Up Week 8 Visit. The LSLV final CSR is produced after the LSLV database lock.

No interim analyses are planned.

2 STUDY DESCRIPTION

2.1 Study Design

The study has 4 phases:

- Observation Phase (OP): Lasts approximately 28 days. Includes the Screening Visit and Pre-randomization Laboratory Visit which must occur within 96 hours of the Baseline Visit.
- Double-blind Treatment (DBT) Phase:
  - Includes the Baseline Visit at which randomization occurs, and Week 2, Week 4, Week 8, Week 12, and End of Treatment (EOT) Visits.
    - Subjects are randomized to 2:2:1:1 to zavegepant 100 mg, zavegepant 200 mg, placebo matching zavegepant 100 mg, or placebo matching zavegepant 200 mg.
    - Randomization is stratified by stable prophylactic migraine medication use through randomization (yes or no).

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  - All randomized subjects who discontinue early from the DBT Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 12 Visit.
  - Subjects are instructed to follow one of the following 2 dosing regimens:
    - Take four (4) 25 mg SGCs of blinded study drug every calendar day, if randomized to the zavegepant 100 mg or placebo matching zavegepant 100 mg treatment group
    - Take eight (8) 25 mg SGCs of blinded study drug every calendar day, if randomized to the zavegepant 200 mg or placebo matching zavegepant 200 mg treatment group.

- Open-label Extension (OLE) Phase:
  - Subjects who (1) complete the DBT Phase, (2) continue to meet all inclusion/exclusion criteria, and (3) have been compliant with the eDiary may enter the OLE Phase, pending review of Week 12 laboratory test results.
  - Subjects are instructed to follow one of the following 2 dosing regimens:
    - Take four (4) 25 mg SGCs of OL zavegepant every calendar day, if randomized to the zavegepant 100 mg or placebo matching zavegepant 100 mg treatment group in the DBT Phase
    - Take eight (8) 25 mg SGCs of OL zavegepant every calendar day, if randomized to the zavegepant 200 mg or placebo matching zavegepant 200 mg treatment group in the DBT Phase.
  - Lasts up to 52 weeks, and includes the Week 14, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, and EOT Visits.
  - All randomized subjects who discontinue early from the OLE Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 64 Visit.

- Follow-up Phase
  - Lasts up to 8 weeks, and includes Follow-up Week 2 and Follow-up Week 8 Visits primarily for safety assessments. These visits should occur approximately 2 weeks and 8 weeks, respectively, after the last visit in the last treatment phase (i.e., Week 12/EOT Visit if the subject did not enter the OLE Phase; Week 64/EOT Visit if the subject entered the OLE Phase).
  - All randomized subjects should complete both follow-up visits, regardless of completing either treatment phase.

The design of the study is shown in Figure 1 and Figure 2. Approximately 2900 subjects are enrolled in order to randomize approximately 1440 subjects.

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Figure 1 Study Schematic: Observation, DBT, and Follow-up Phases

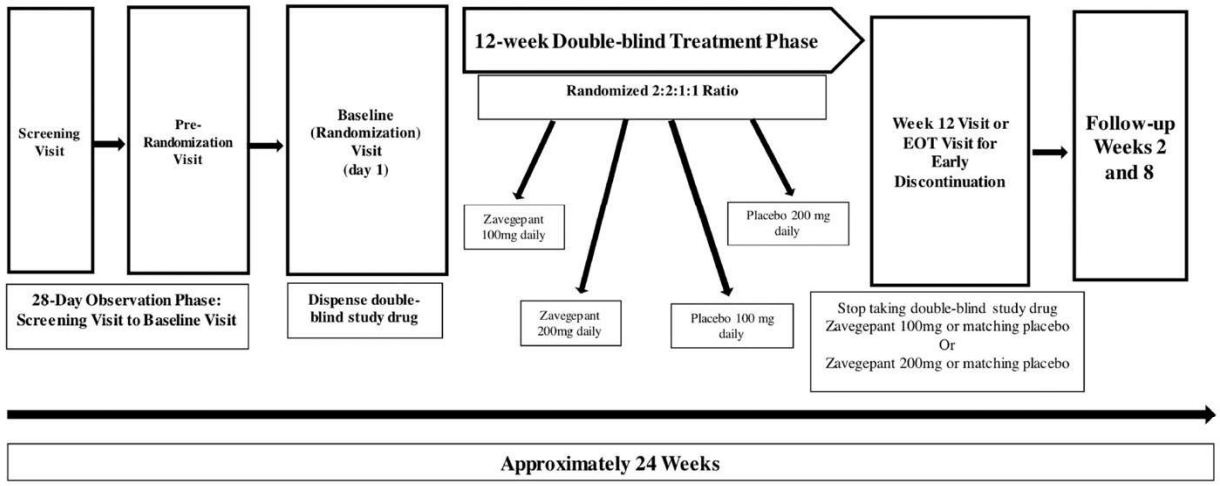
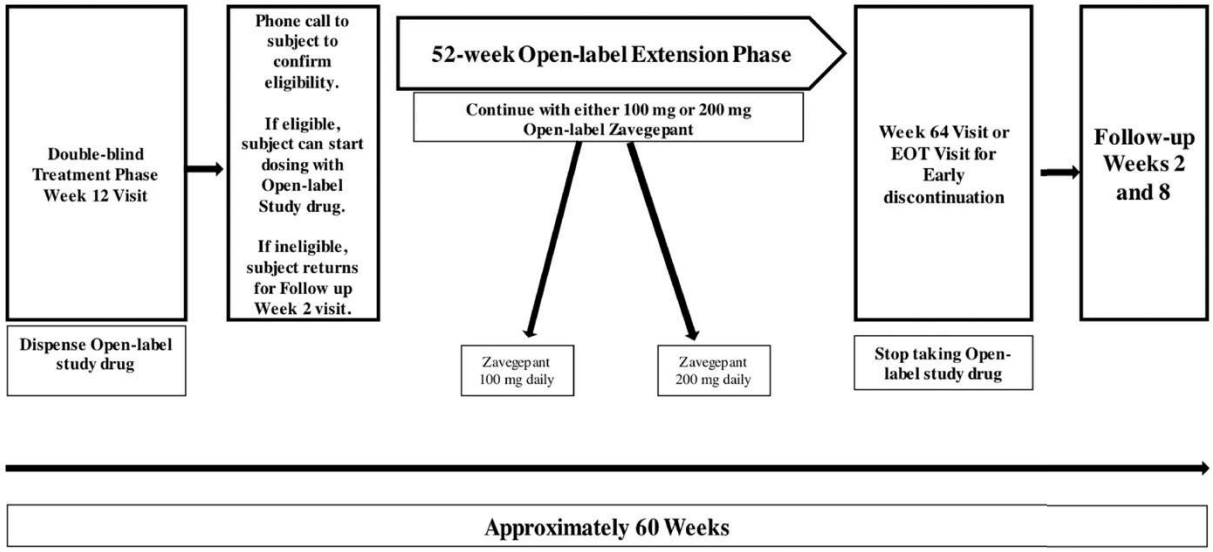


Figure 2 Study Schematic: OLE and Follow-up Phases



2.2 Treatment Assignment

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

The IWRS randomizes eligible subjects to a treatment group (see Section 2.1) using permuted blocks of size 12 at the Baseline Visit. Randomization is stratified by stable prophylactic migraine medication use through randomization (yes or no).

The IWRS also assigns specific container numbers for study drug to be dispensed at the Baseline Visit and subsequent visits in the DBT and OLE Phases.

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2.3 Blinding and Unblinding

This study is blinded to study drug active status (zavegepant versus placebo), but not to the dose level (100 or 200 mg), through the LSLV database lock (see Section 1.2). Draft TLFs for the LSLV final CSR are produced with dummy treatment groups prior to the LSLV database lock. TLFs for the LSLV final CSR are produced unblinded.

2.4 Protocol and Protocol Amendments

BHV3500-302 SAP Versions 1 and 2 are based on BHV3500-302 Protocol Version 4 (28-Jun-2021).

BHV3500-302 SAP Versions 3 and 4 are based on BHV3500-302 Protocol Version 5 (16-Nov-2021), which added the OLE Phase and 2 exploratory objectives.

BHV3500-302 SAP Versions 5, 6, 7, 8, and 9 are based on BHV3500-302 Protocol Version 6 (16-May-2022), which modified the language in efficacy objectives and endpoints (i.e., changed "baseline" to "the OP") and added 1 exploratory objective.

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

A month is defined as 4 weeks (28 days) for the purpose of this protocol.

3.1.1 Primary Objective

To compare the efficacy of zavegepant to placebo as a preventive treatment for chronic migraine, as measured by the mean reduction from the OP in the number of migraine days per month over the entire DBT Phase.

3.1.2 Secondary Objectives

1. To compare zavegepant to placebo on the proportion of subjects with ≥ 50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase.
2. To compare the efficacy of zavegepant to placebo on the mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase.
3. To compare the efficacy of zavegepant to placebo on the mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase.
4. To compare the efficacy of zavegepant to placebo on the mean number of acute migraine-specific medication days per month over the entire DBT Phase.
5. To compare the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the DBT Phase between zavegepant and placebo.

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6. To compare the mean change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 of the DBT Phase between zavegepant and placebo.
7. To evaluate the safety and tolerability of zavegepant during the DBT and OLE Phases.
8. To evaluate the frequency of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal (ULN) concurrent with total bilirubin (TBL) > 2x ULN in subjects treated with zavegepant during the DBT and OLE Phases.
9. To evaluate the frequencies of hepatic-related adverse events (AEs) and hepatic-related AEs leading to study drug discontinuation in subjects treated with zavegepant during the DBT and OLE Phases.

3.1.3 Exploratory Objectives

1. To compare the efficacy of zavegepant to placebo on the mean reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.
2. To compare the efficacy of zavegepant to placebo on the proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.
3. To compare the efficacy of zavegepant to placebo on the mean reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each of the first 4 weeks of the DBT Phase.
4. To compare the efficacy of zavegepant to placebo on the proportion of subjects with ≥ 50% reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.
5. To compare the efficacy of zavegepant to placebo on the proportions of subjects with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.
6. To compare the efficacy of zavegepant to placebo on the mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase.
7. To compare the efficacy of zavegepant to placebo on the mean number of acute migraine medication days per month in each month and over the entire DBT Phase.
8. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, or TBL) based on fold changes above ULN in subjects treated with zavegepant during the DBT and OLE Phases.
9. To evaluate the frequency of ALT or AST elevations > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with zavegepant during the DBT and OLE Phases.

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10. To compare the mean changes from baseline in the MSQ preventive role function and emotional function domain scores at Week 12 of the DBT Phase between zavegepant and placebo.
11. To compare the mean changes from baseline in the MIDAS absenteeism and presenteeism scores at Week 12 of the DBT Phase between zavegepant and placebo.
12. To evaluate the mean changes from baseline in MSQ domain scores and MIDAS scores during the OLE Phase.
13. To evaluate the Preference of Medication (PoM) scale during the DBT and OLE Phases.
14. To evaluate the Satisfaction with Medication (SM) scale during the DBT and OLE Phases.
15. To evaluate the Clinical Global Impression – change (CGI-c) scale during the DBT and OLE Phases.
16. To evaluate the pharmacokinetics of zavegepant 100 mg and 200 mg.

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.

For efficacy and outcomes research endpoints, treatment group comparisons are based on zavegepant 100 mg verses placebo pooled and zavegepant 200 mg verses placebo pooled.

Intercurrent Events

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation.

Study drug discontinuation before the time point of interest defining the endpoint is considered an intercurrent event.

- For efficacy objectives assessed with a continuous endpoint during the DBT Phase, study drug discontinuation is handled with a "hypothetical strategy," i.e., the hypothetical scenario is that had subjects not discontinued DB study drug, their efficacy would have been similar to the efficacy of subjects from the same treatment group and randomization stratum who did not discontinue DB study drug. All observed values of the endpoint of interest are excluded after DB study drug discontinuation (see Section 7.2), and statistical methods are used to estimate the treatment effect that would have been seen had the intercurrent event not occurred.

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- For efficacy objectives assessed with a binary endpoint during the DBT Phase, DB study drug discontinuation is handled with a "composite strategy," i.e., the occurrence of the intercurrent event is integrated as a component of the endpoint. All observed values of the endpoint of interest are excluded after DB study drug discontinuation (see Section 7.2), and subjects with missing data are considered failures.
- For safety objectives, study drug discontinuation is handled with a "while-on-treatment strategy". All observed values of the endpoint of interest are used on or before study drug discontinuation + 7 days (see Section 7.2 and the Core SAP).
- For outcomes research and other objectives, study drug discontinuation is handled with a "treatment policy strategy", i.e., the occurrence of the intercurrent event is considered irrelevant, such that all observed values of the endpoint of interest are used regardless of study drug discontinuation.

Non-study prophylactic migraine medication use before the time point of interest defining the endpoint is also considered an intercurrent event. For all objectives, this intercurrent event is handled with a treatment policy strategy, such that all observed values of the endpoint of interest are used.

Nonstudy acute migraine-specific medication use before the time point of interest defining the endpoint is also considered an intercurrent event, except for efficacy objectives based on acute migraine-specific medication days or acute migraine medication days.

- For efficacy objectives based on migraine days, this intercurrent event is handled with a composite strategy, such that acute migraine-specific medication use is part of the endpoint definition of migraine days.
- For safety and outcomes research objectives, this intercurrent event is handled with a treatment policy strategy, such that all observed values of the endpoint of interest are used.

Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura before the time point of interest defining the endpoint is also considered an intercurrent event, except for the efficacy objective based on acute migraine medication days. For all objectives, this intercurrent event is handled with a treatment policy strategy, such that all observed values of the endpoint of interest are used.

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

Data Sources for Endpoints

Migraine days, acute migraine-specific medication days, acute migraine medication days, and headache days are derived from eDiary data from the external source YPrime. Acute migraine-specific medications are triptans and ergotamine. Acute migraine medications are triptans, ergotamine, and other protocol-allowed medications to treat headache or aura taken on migraine days.

AEs are determined from AE case report forms (CRFs).

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Grade 3 to 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria. Laboratory test results are from an external central laboratory and local laboratory test CRFs.

C-SSRS parameters, MSQ scores, and MIDAS scores are derived from their respective CRFs.

3.2.1 Primary Objective Estimand

The estimand corresponding to the primary endpoint is shown in Table 1.

Table 1 Primary Objective Estimands

Objective	**Mean reduction from the OP in the number of migraine days per month over the entire DBT Phase**
Efficacy Endpoint	Mean change from OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12)
Summary	Mean change from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

3.2.2 Secondary Objective Estimands

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

Table 2 Secondary Objective Estimands

Objective 1	**Proportion of subjects with ≥ 50% reduction from the OP in the number of moderate or severe migraine days per month over the entire DBT Phase**
Efficacy Endpoint	Proportion of subjects with ≥ 50% reduction from OP in number of moderate or severe migraine days per month over the entire DBT Phase (Weeks 1 to 12)
Summary	Percentages by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation with stratification by randomization stratum for the migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 2	**Mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase**

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Efficacy Endpoint	Mean change from OP in the mean number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase
Summary	Mean change from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 3	**Mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase**
Efficacy Endpoint	Mean change from OP in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase
Summary	Mean change from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 4	**Mean number of acute migraine-specific medication days per month over the entire DBT Phase**
Efficacy Endpoint	Mean number of acute-migraine-specific days per month over the entire DBT Phase (Weeks 1 to 12)
Summary	Mean value by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: not applicable
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 5	**Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear regression model, and difference between treatment groups from model for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy
	Non-study prophylactic migraine medication use: treatment policy strategy

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	Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 6	**Mean change from baseline in the MIDAS total score at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean change from baseline in the MIDAS total score at Week 12 of the DBT Phase
Summary	Mean change from baseline by treatment group using descriptive statistics and linear regression model and difference between treatment groups from model for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 7	**Safety and tolerability of zavegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AEs by intensity, serious adverse events (SAEs), AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities on treatment
Summary	Frequency by treatment group for the DBT and OL zavegepant safety analysis sets
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 8	**Frequency of ALT or AST > 3x upper limit of normal (ULN) concurrent with TBL > 2x ULN in subjects treated with zavegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with AST or ALT elevations > 3x ULN concurrent (i.e., on the same laboratory collection date) with TBL > 2x ULN on treatment
Summary	Frequency by treatment group for the DBT and OL zavegepant safety analysis sets with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
	Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 9	**Frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation in subjects treated with zavegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment
Summary	Frequency by treatment group for the DBT and OL zavegepant safety analysis sets

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Intercurrent Events	Study drug discontinuation: while-on-treatment strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: treatment policy strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

3.2.3 Exploratory Objective Estimands

The estimands corresponding to the exploratory objectives are shown in Table 3 only for the endpoints to be assessed.

Table 3 Exploratory Objective Estimands

Objective 1	**Mean reduction from the OP in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase**
Efficacy Endpoint	Mean changes from OP in the number of migraine days per month during DBT (1) over time by month and (2) overall DBT, by pain intensity (total; moderate or severe)
Summary	Mean changes from OP by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 2	**Proportions of subjects with ≥ 50% reduction from the OP in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase**
Efficacy Endpoint	Proportions of subjects with ≥ 50% reduction from the OP in the number of migraine days per month during DBT (1) over time by month and (2) overall DBT, by pain intensity (total; moderate or severe)
Summary	Percentages by treatment group, and difference in percentages between treatment groups using Mantel-Haenszel risk estimation with stratification by randomization stratum for the migraine analysis set
Intercurrent Events	Study drug discontinuation: composite strategy
	Non-study prophylactic migraine medication use: treatment policy strategy
	Nonstudy acute migraine-specific medication use: composite strategy
	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 6	**Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase**
Efficacy Endpoint	Mean number of acute migraine-specific medication days per month during DBT (1) over time by month and (2) overall DBT

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Summary	Mean values by treatment group using descriptive statistics and linear mixed effects model with repeated measures, and difference between treatment groups from model for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: not applicable Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 7	**Mean number of acute migraine medication days per month in each month and over the entire DBT Phase**
Efficacy Endpoint	Mean number of acute migraine medication days per month during DBT (1) over time by month and (2) overall DBT
Summary	Mean values by treatment group using descriptive statistics for the migraine analysis set
Intercurrent Events	Study drug discontinuation: hypothetical strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: not applicable Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: not applicable
Objective 8	**Frequency of LFT elevations based on fold changes above ULN in subjects treated with zavegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects with LFT elevations (ALT, AST, or TBL) based on fold changes above ULN on treatment
Summary	Frequency by treatment group for the DBT and OL zavegepant safety analysis sets with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 9	**Frequency of ALT or AST elevations > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with zavegepant during the DBT and OLE Phases**
Safety Endpoint	Number and percentage of subjects in the safety analysis set with ALT or AST > 3x ULN concurrent with nausea, vomiting, anorexia, abdominal pain or fatigue on treatment
Summary	Frequency by treatment group for the DBT and OL zavegepant safety analysis sets with LFT data
Intercurrent Events	Study drug discontinuation: while-on-treatment strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy

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	Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 10	**Mean changes from baseline in the MSQ preventive role function and emotional function domain scores at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean changes from baseline in the MSQ preventive role function and emotional function domain scores at Week 12 of the DBT Phase
Summary	Mean changes from baseline by treatment group using descriptive statistics for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 11	**Mean changes from baseline in the MIDAS absenteeism and presenteeism scores at Week 12 of the DBT Phase**
Outcomes Research Endpoint	Mean changes from baseline in the MIDAS absenteeism and presenteeism scores at Week 12 of the DBT Phase
Summary	Mean changes from baseline by treatment group using descriptive statistics for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy
Objective 12	**Mean changes from baseline in MSQ domain scores and MIDAS scores during the OLE Phase**
Outcomes Research Endpoint	Mean changes from baseline in the (1) MSQ restrictive role function, preventive role function, and emotional function domain scores and (2) MIDAS total, absenteeism, and presenteeism scores at Weeks 24 and 64 of the OLE Phase
Summary	Mean changes from baseline by treatment group using descriptive statistics for the DBT efficacy analysis set
Intercurrent Events	Study drug discontinuation: treatment policy strategy Non-study prophylactic migraine medication use: treatment policy strategy Nonstudy acute migraine-specific medication use: treatment policy strategy Use of nonstudy other medication to treat headache (migraine or nonmigraine) or aura: treatment policy strategy

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

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

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- Enrolled: Subjects who sign an informed consent form and are assigned a subject identification number, i.e., nonmissing informed consent date. This analysis set is used mainly to assess study population and in by-subject listings.
- Full: Subjects in the enrolled analysis set who receive a randomized treatment assignment from the IWRS, i.e., nonmissing IWRS randomization date. This analysis set is used mainly to assess study population.
- Safety: Subjects in the enrolled analysis set who take ≥ 1 dose of study drug (zavegepant or placebo), i.e., nonmissing study drug start date. This analysis set is used to assess study population and produce select by-subject listings.
    - DBT safety: Subjects in the safety analysis set who take ≥ 1 dose of DB study drug (zavegepant or placebo), i.e., nonmissing DB study drug start date. This analysis set is used to assess study population, exposure, and on-DBT safety.
    - OL zavegepant safety: Subjects in the safety analysis set who take ≥ 1 dose of OL zavegepant, i.e., nonmissing OL zavegepant start date. This analysis set is used to assess study population, exposure, and on-OL zavegepant safety.
        - Interim safety: Subjects in the OL zavegepant safety analysis set with OL zavegepant start date – DB study drug last date > 7 days. This analysis set is used to assess post-DBT pre-OL zavegepant safety.
    - DB or OL zavegepant safety: Subjects in the safety analysis set who take ≥ 1 dose of DB or OL zavegepant, i.e., nonmissing DB or OL zavegepant start date. This analysis set is used to assess exposure and on-DB or OL zavegepant safety.
    - Follow-up safety: Subjects in the safety analysis set whose last contact date is in the follow-up safety analysis period. This analysis set is used to assess follow-up safety.
- DBT efficacy: Subjects in the full analysis set who are randomized only once and take ≥ 1 dose of DB study drug (zavegepant or placebo). This analysis set is used mainly to assess DBT outcomes research.

    Migraine: Subjects in the DBT efficacy analysis set with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and ≥ 1 month (4-week interval) in the DBT Phase (see Section 6.3.1). This analysis set is used to assess migraine days, acute migraine-specific medication days, and acute migraine medication days

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

4.2 Treatment Groups

Treatment groups in the DBT Phase are zavegepant 100 mg, zavegepant 200 mg, placebo 100 mg, and placebo 200 mg. OL zavegepant dose groups in the OLE Phase are zavegepant 100 mg and zavegepant 200 mg.

The safety analysis sets are assessed by as-treated treatment group (i.e., actual treatment received), the randomized, full, efficacy, and migraine analysis sets are assessed by as-randomized treatment group, and the enrolled analysis set is assessed overall.

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If a subject takes ≥ 1 dose of planned randomized DB study drug, then that subject is considered to have as-treated treatment group equal to as-randomized treatment group (see Section 6.2.6.2).

If there are non-randomized subjects who take study drug, then the as-randomized treatment group of "not randomized" is included in the full analysis set augmented with the safety analysis set.

4.3 Subgroups

The following efficacy subgroups are of interest for the migraine analysis set:

- Stable prophylactic migraine medication use through randomization (i.e., randomization stratum): yes, no (see Section 6.2.5.4).

Randomization strata are based on the actual data, not those assigned by IWRS. Subgroup tables present results by subgroup level and overall for subjects with nonmissing subgroup level data.

5 SAMPLE SIZE, POWER, AND TYPE 1 ERROR

With a sample size of approximately 480 randomized subjects per zavegepant treatment group and 240 randomized subjects per placebo treatment group, we expect approximately 440 subjects per zavegepant treatment group and 220 subjects per placebo treatment group in the migraine analysis set. Assuming zavegepant provides a 1-day advantage over placebo pooled on the mean change in migraine days per month over the entire DBT Phase (Weeks 1 to 12), common standard deviation of 4.2 days, and a 2-sided $\alpha = 0.025$ level, then the study has ≥ 90% power for the primary endpoint. The estimates for the migraine analysis set sample size, mean change in migraine days per month, and standard deviation (SD) are based on observed pooled data from rimegepant study BHV3000-305.

Type 1 error is not applicable. The significance of the primary and secondary endpoints will not be evaluated.

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 Core SAP for additional details about programmed output.

6.1.1.1 Tables

Treatment group presentation in tables by analysis set is shown in Table 4. Exceptions are specified in subsequent sections as needed.

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Table 4 Treatment Group Presentation in Tables by Analysis Set

Analysis Set	Number of Columns	Abbreviated Treatment Group
Enrolled	1	Overall
Full, DBT efficacy, migraine, DBT safety, interim safety by treatment group, {zavegepant pooled}, {placebo pooled}, and {overall}	4 to 7	ZAV 100 mg ZAV 200 mg {ZAV Pooled} PBO 100 mg PBO 200 mg {PBO Pooled} {Overall}
OL zavegepant safety by OL zavegepant dose and overall	3	OL ZAV 100 mg OL ZAV 200 mg Overall
DB or OL zavegepant safety by DB or OL zavegepant dose and overall	3	DB ZAV or PBO 100 mg/OL ZAV 100 mg DB ZAV or PBO 200 mg/OL ZAV 200 mg Overall
Follow-up safety by treatment group/OL zavegepant status and overall	6	DB ZAV 100 mg/OL ZAV 100 mg DB ZAV 200 mg/OL ZAV 200 mg DB PBO 100 mg to OL ZAV 100 mg DB PBO 200 mg to OL ZAV 200 mg DB PBO Pooled No OL ZAV Overall

"ZAV Pooled" is defined as the DB zavegepant 100 mg and DB zavegepant 200 mg treatment groups combined. "PBO Pooled" is defined as the DB placebo 100 mg and DB placebo 200 mg treatment groups combined. "DB PBO *X* mg to OL ZAV *X* mg" denotes as-treated DB placebo *X* mg subjects in the OL zavegepant safety analysis set (*X* = 100 or 200), and "DB PBO Pooled No OL ZAV" denotes as-treated DB placebo pooled subjects not in the OL zavegepant safety analysis set; note that these 3 placebo groups add to the "PBO Pooled" group.

Results for study population also include overall treatment group (see Sections 6.2 and 6.4).

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 abbreviated as (1) "ZAV100" for zavegepant 100 mg, "ZAV200" for zavegepant 200 mg, "PBO100" for placebo 100 mg, and "PBO200" for placebo 200 mg for subjects in the full analysis set, and (2) "NRND" for subjects not in the full analysis set.

Listings of significant protocol deviations, exposure, safety parameters, and outcomes research parameters include the following: abbreviated name of the analysis period in which the measurement was slotted (i.e., PRETRT, DBT, INT, OLZAV, FU; this does not apply to exposure); analysis visit in which the measurement was slotted (this does not apply to exposure

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or AEs); measurement date/time; study day derived from the measurement date, and zavegepant study day ≥ 1 derived from the measurement date for as-randomized placebo subjects.

6.1.2 Statistical Methods

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

6.1.3 Missing Data

All analyses are based on observed data unless otherwise specified. See Section 6.3 for statistical methods for handling missing data in efficacy analyses.

6.2 Study Population

Refer to the Core SAP for TLF contents.

6.2.1 Analysis Sets

The frequency table of analysis sets described in Section 4.1 is provided by treatment group plus placebo pooled (as-randomized for the randomized, full, efficacy, and migraine analysis sets; as-treated for all safety analysis sets), not randomized, and overall.

See Section 6.3.1 for months.

The by-subject listing of analysis sets is provided for the enrolled analysis set.

The administrative listing of randomization scheme and codes is provided for the full analysis set.

6.2.2 Enrollment

Frequency table of enrollment by country and site is provided for the enrolled analysis set, and also displays results for the full and safety analysis sets.

6.2.3 Subject Disposition

The by-subject listing of subject discontinuation is provided for the enrolled analysis set and displays a separate record for each study phase (i.e., DBT, OLE and Follow-up) that is discontinued (i.e., completed or not completed) corresponding to each type of subject status CRF. The listing includes the following:

- Relevant reference dates: i.e., last contact date*, IWRS randomization date
- Study phase: DBT, OLE, or Follow-up. For each study phase:
    - Last visit date. Derived from visit dates from the Visit Date and Unscheduled Visit Checklist CRFs as follows:
        - DBT Phase: latest visit date in the pretreatment or on-DBT safety analysis period

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  - OLE Phase: latest visit date in the OL zavegepant safety analysis period
  - Follow-up Phase: latest visit date in the follow-up safety analysis period
- Phase completion status: "completed"; or "not completed" concatenated with the reason for non-completion (see Sections 6.2.3.1, 6.2.3.2, 6.2.3.3, 6.2.3.4, and 6.2.3.5)
- Next phase continuation status: "continued" concatenated with the name of the next phase (OLE or Follow-up); or "not continued" concatenated with the reason for non-continuation (see Sections 6.2.3.2, 6.2.3.3, and 6.2.3.4). This does not apply to the Follow-up Phase.

A footnote describes the derivation of the last contact date as "* Derived as the death date (if it exists); otherwise, the maximum date collected across study population, efficacy safety, and outcomes research parameters". See Section 7.1 for derived dates and Section 7.2 for analysis periods.

6.2.3.1 Subject Disposition from Enrollment to Randomization

The frequency table of subject disposition from enrollment to randomization is provided for the enrolled analysis set based on the DB Subject Status CRF, and displays the following categories:

- Randomized (identified as subjects with nonmissing IWRS randomization date)
- Not randomized (identified as subjects with missing IWRS randomization date)
  - Reasons for discontinuation (i.e., not completing the DBT Phase), including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure from the Inclusion/Exclusion CRF are also displayed as subcategories.

6.2.3.2 Subject Disposition from Randomization to Treatment

The frequency table of subject disposition from randomization to treatment is provided by treatment group and overall for the full analysis set based on the DB Subject Status CRF, and displays the following categories:

- Treated with study drug (identified as subjects with nonmissing study drug start date)
- Not treated with study drug (identified as subjects with missing study drug start date)
  - Reasons for discontinuation (i.e., not completing the DBT Phase), including not reported

6.2.3.3 Subject Disposition during the DBT Phase

The frequency table of subject disposition during the DBT Phase is provided for the DBT safety analysis set by as-treated treatment group, zavegepant pooled, placebo pooled, and overall based on the DB Subject Status CRF, and displays the following categories:

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- Ongoing in the DBT Phase. These are identified as subjects with (1) missing response to the question "Did the subject complete the DBT Phase?" and (2) missing DB study drug last date. This category only exists before the LSLV database lock. After the LSLV database lock, subjects with missing response are categorized as "Did not complete the DBT Phase".
- Completed the DBT Phase. These are identified as subjects with (1) "yes" response to the question "Did the subject complete the DBT Phase?" and (2) nonmissing DB study drug last date.
- Did not complete the DBT Phase. These are identified as subjects with (1) "no" or missing response to the question "Did the subject complete the DBT Phase?" and (2) nonmissing DB study drug last date.
    - Reasons for not completing the DBT Phase, including not reported
- Continued to the next phase. These are identified as subjects with (1) "yes" response to the question "Is the subject continuing to the Follow-up Phase?" and missing response to the question "Is the subject continuing to the next phase?", or (2) "yes" response to the question "Is the subject continuing to the next phase?".
    - Next phase, i.e., OLE or Follow-up. The next phase is determined from the response to the "If Yes, select the next phase" question, if available. Otherwise, if there is a "yes" response to the question "Is the subject continuing to the Follow-up Phase?", then the next phase is considered to be Follow-up.
- Did not continue to the next phase. These are identified as subjects with (1) missing response to the question "Is the subject continuing to the next phase?" and "no" response to the question "Is the subject continuing to the Follow-up Phase?", or (2) "no" response to the question "Is the subject continuing to the next phase?", or (3) after the LSLV database lock, missing responses to both questions about continuing.
    - Reasons for not continuing to the next phase, including not reported. These are based on reasons for not continuing to the Follow-up Phase or the next phase.

6.2.3.4 Subject Disposition during the OLE Phase

The frequency table of subject disposition during the OLE Phase is provided by OL zavegepant dose and overall for the OL zavegepant safety analysis set based on the OLE Subject Status CRF, and displays the following categories:

- Ongoing in the OLE Phase. These are identified as subjects with (1) missing response to the question "Did the subject complete the OLE Phase?" and (2) missing OL zavegepant last date. This category only exists before the final database lock; otherwise, subjects with missing response are categorized as "Did not complete the OLE Phase".
- Completed the OLE Phase. These are identified as subjects with (1) "yes" response to the question "Did the subject complete the OLE Phase?" and (2) nonmissing OL zavegepant last date.

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- Did not complete the OLE Phase. These are identified as subjects with (1) "no" or missing response to the question "Did the subject complete the OLE Phase?" and (2) nonmissing OL zavegepant last date.
  - Reasons for not completing the OLE Phase, including not reported
- Continued to the Follow-up Phase. These are identified as subjects with "yes" response to the question "Is the subject continuing to the Follow-up Phase?".
- Did not continue to the Follow-up Phase. These are identified as subjects with (1) "no" response to the question "Is the subject continuing to the Follow-up Phase?", or (2) after the LSLV database lock, missing response to the question "Is the subject continuing to the Follow-up Phase?".
  - Reasons for not continuing to the Follow-up Phase, including not reported.

6.2.3.5 Subject Disposition during the Follow-up Phase

The frequency table of subject disposition during the Follow-up Phase is provided by as-treated treatment group/OL zavegepant status and overall for the follow-up safety analysis set based on the Follow-up Subject Status CRF, and displays the following categories:

- Did not formally enter the Follow-up Phase. These are identified as subjects with missing response to the question "Did the subject complete the Follow-up Phase?", and any of the following:
  - "No" response to the question "Is the subject continuing to the Follow-up Phase?" and missing response to the question "Is the subject continuing to the next phase?" on the DB Subject Status CRF
  - "No" response to the question "Is the subject continuing to the next phase?" on the DB Subject Status CRF
  - "No" response to the question "Is the subject continuing to the Follow-up Phase?" on the OLE Subject Status CRF.

  A footnote explains that these are subjects with data in the follow-up safety analysis period who did not continue to the Follow-up Phase as per DB or OLE Subject Status CRF.
- Ongoing in the Follow-up Phase. These are identified as subjects with missing response to the question "Did the subject complete the Follow-up Phase?", and who are not already categorized as "Did not formally enter the Follow-up Phase".

  This category only exists before the final database lock. After the final database lock, these subjects are categorized as "Did not complete the Follow-up Phase".
- Completed the Follow-up Phase. These are identified as subjects with "yes" response to the question "Did the subject complete the Follow-up Phase?".
- Did not complete the Follow-up Phase. These are identified as subjects with "no" response to the question "Did the subject complete the Follow-up Phase?".

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- Reasons for not completing the Follow-up Phase, including not reported
-

6.2.4 Protocol Deviations

6.2.4.1 Relevant Protocol Deviations

The frequency table of relevant protocol deviations are provided as the number and percentage of subjects in deviation categories by as-randomized treatment group, zavegepant pooled, placebo pooled, 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 9.1. 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 full analysis set. This includes deviation type, category, and subcategory, which are additional sorting variables.

6.2.4.2 Significant Protocol Deviations

The by-subject listing of significant protocol deviations is provided for the full analysis set, and is based on the Protocol Deviations CRF. This includes date deviation occurred, violation code, inclusion/exclusion number, and description, which are additional sorting variables. Significant protocol deviations are defined as those with a "yes" response to the question "Is the deviation significant?".

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, and efficacy during the OP), (3) medical history, and (4) non-study prior medications. These are detailed in Sections 6.2.5.1 through 6.2.5.4, respectively.

Tables of baseline characteristics are provided for the following analysis sets:

- Migraine analysis set: Baseline characteristics (1) and (2) by as-randomized treatment group, placebo pooled, and overall to support efficacy
- DBT safety analysis set: Baseline characteristics (1) through (4) by as-treated treatment group, zavegepant pooled, placebo pooled, and overall to support safety
- OL zavegepant safety analysis set: Demographics and other relevant baseline characteristics by OL zavegepant dose and overall to support OL zavegepant safety

The frequency cross table of randomization stratum (i.e., stable prophylactic migraine medication use through randomization [yes, no]) from IWRS versus actual data is provided for the full analysis set by treatment group and overall (see Section 6.2.5.4).

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Baseline for a parameter (e.g., weight) is defined according to analysis set; refer to the Core SAP for details, including handling of ties on the same measurement date (entry date/time is the "earliest data creation time" variable in the raw CRF datasets). Note that the baseline value is independent of the baseline analysis visit defined in Table 5; the latter is used only in by-subject listings that display visit.

By-subject listings are provided for the enrolled analysis set for the following: demographics; medical history; and migraine history.

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Refer to the Core SAP for the table of demographics and other relevant baseline characteristics. Other relevant characteristics also include the following categorical variables:

- Previous study participation (e.g., any study, BHV3500-201, BHV3500-301)
- Randomization stratum based on actual data − stable prophylactic migraine medication use through randomization: yes, no (see Section 6.2.5.4).

6.2.5.2 Baseline Disease Characteristics

Migraine History

Refer to the Core SAP for the table of migraine history.

Cardiac and Other Risk Factors

Refer to the Core SAP for the table of cardiac and other risk factors, which is provided only for the DBT safety analysis set.

Migraine-related Event Days during the OP

The table of migraine-related event days per month during the OP is provided only for the migraine analysis set, and summarizes the following parameters descriptively as continuous or categorical variables during the OP analysis period:

- Migraine days per month by pain intensity (total; moderate or severe). Categories are < 6, $\geq 6, < 8, \geq 8, < 12, \geq 12, < 15, \geq 15$.
- Acute migraine-specific medication days per month. Categories are same as for migraine days per month above.
- Acute migraine medication days per month. Categories are same as for migraine days per month above.

See Sections 6.3.1 for migraine days per month, Section 6.3.2.2 for acute migraine-specific medication days per month, Section 6.3.3.6 for acute migraine medication days per month, and Section 7.2 for the OP analysis period.

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

6.2.5.3 Medical History

The frequency table of medical history is provided by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency within SOC and PT.

6.2.5.4 Non-study Prior Medications

Frequency tables of the following non-study medications are provided by therapeutic class and preferred name:

- Current medications: all; acute migraine; 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 6.2.6.3.

Stable medications through randomization are defined as those taken > 12 weeks before informed consent and through randomization, i.e., (1) informed consent date – imputed medication start date > 84 days, and (2) IWRS randomization date ≤ imputed medication end date.

6.2.6 Exposure

Analyses are based on as-treated treatment group to support safety, unless specified otherwise.

6.2.6.1 Study Medication

During the DBT Phase, study drug is zavegepant 100 mg, zavegepant 200 mg, or matching placebo daily; subjects take four (4) to eight (8) 25 mg SGCs daily, depending on their randomized treatment assignment.

During the OLE Phase, study drug is zavegepant 100 or 200 mg; subjects take four (4) to eight (8) 25 mg SGCs daily, depending on their randomized treatment assignment in the DBT Phase.

Study drug is dispensed in a wallet-type blister card with a unique wallet ID. Each wallet has 8 rows of 4 capsules for a total of 32 capsules. Sites report the wallet ID, study medication start date, study medication end date, and number of capsules taken on the IP Dosing CRF. Wallet IDs are 5 digits for DB study drug and 6 digits for OL zavegepant.

The kit type identifier associated with a wallet ID is DB zavegepant 100 mg, DB zavegepant 200 mg, DB placebo 100 mg, DB placebo 200 mg, OL zavegepant 100 mg, or OL zavegepant 200 mg, and is obtained by merging the IP Dosing CRF data with the DB study drug kit list file data and OL zavegepant kit list file data by wallet ID.

The by-subject listing of study drug is provided for the safety analysis set, and presents study medication start date, study medication end date, study day derived from study medication start

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date, number of capsules taken ≥ 0, wallet ID, and kit type identifier. The listing also displays DB study drug start and end dates, OL zavegepant start and end dates, displays study drug exposure parameters (time on DBT, time on OL zavegepant, time on DB or OL zavegepant), and identifies invalid wallet IDs. Valid DB wallet IDs are those in the DB study drug kit list file. Valid OL wallet IDs are those in the OL zavegepant kit list file. The listing is sorted by site-subject ID, study medication start date, study medication end date, and wallet ID.

DB Study Drug Exposure

The table of DB study drug exposure is provided descriptively by treatment group, zavegepant pooled, and placebo pooled for the DBT safety analysis set, and summarizes the following parameters descriptively as continuous or categorical variables:

- Time on DB study drug (weeks), derived as (DB study drug end date – DB study drug start date + 1)/7
- Time on DB study drug (weeks) categories: < 2, ≥ 2 to < 4, ≥ 4 to < 6, ≥ 6 to < 8, ≥ 8 to < 10, ≥ 10 to < 12, ≥ 12
- Cumulative DB study drug exposure (mg), derived by summing {number of days × number of capsules taken per day × dose} across records with complete study medication start date and valid DB wallet ID
    - Number of days for a record is derived as imputed study medication end date – study medication start date + 1.
    - The dose is 25 mg if the kit type identifier is DB zavegepant 100 or 200 mg; otherwise, the dose is 0.
- Average DB study drug exposure (mg per day), derived as cumulative DB study drug exposure/time on DB study drug (days)
- Total DB study drug exposure (capsules) summed across all subjects, derived by summing cumulative DB study drug exposure across all subjects
- Total DB study drug exposure (patient-years), derived by summing (DB study drug end date – DB study drug start date + 1)/365.25 across all subjects.

OL Zavegepant Exposure

The table of OL zavegepant exposure is provided descriptively by OL zavegepant dose and overall for the OL zavegepant safety analysis set, and summarizes the following parameters descriptively as continuous or categorical variables:

- Time on OL zavegepant (weeks), derived as (OL zavegepant end date – OL zavegepant start date + 1)/7
- Time on OL zavegepant (weeks) categories: ≤ 12, ≤ 24, > 24
- Time on OL zavegepant milestone categories:

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  - ≥ 3 months, defined as ≥ 11 weeks
  - ≥ 6 months, defined as ≥ 23 weeks
  - ≥ 1 year, defined as ≥ 51 weeks.
- Cumulative OL zavegepant exposure (mg), derived by summing {number of days × number of capsules taken per day × 25} across records with complete study medication start date and valid OL wallet ID
- Average OL zavegepant exposure (mg per day), derived as cumulative OL zavegepant exposure/time on OL zavegepant (days)
- Total OL zavegepant exposure (capsules) summed across all subjects, derived by summing cumulative DB exposure across all subjects
- Total OL zavegepant exposure (patient-years), derived by summing (OL zavegepant end date – OL zavegepant start date + 1)/365.25 across all subjects.

DB or OL Zavegepant Exposure

The table of DB or OL zavegepant exposure is provided descriptively by DB or OL zavegepant dose and overall for the DB or OL zavegepant safety analysis set, and summarizes the following parameters descriptively as continuous or categorical variables:

- Time on DB or OL zavegepant (weeks), derived as (DB or OL zavegepant end date – DB or OL zavegepant start date + 1)/7
- Time on DB or OL zavegepant (weeks) categories: ≤ 12, ≤ 24, > 24
- Time on DB or OL zavegepant milestone categories:
  - ≥ 3 months, defined as ≥ 11 weeks
  - ≥ 6 months, defined as ≥ 23 weeks
  - ≥ 1 year, defined as ≥ 51 weeks
  - ≥ 15 months, defined as ≥ 63 weeks.
- Cumulative DB or OL zavegepant exposure (mg), derived as {number of days × number of capsules taken per day × 25} across records with complete study medication start date and kit type identifier of DB zavegepant 100 mg, DB zavegepant 200 mg, OL zavegepant 100 mg, or OL zavegepant 200 mg
- Average DB or OL zavegepant exposure (mg per day), derived as cumulative DB or OL zavegepant exposure/time on DB or OL zavegepant drug (days)
- Total DB or OL zavegepant exposure (capsules) summed across all subjects, derived by summing cumulative DB exposure across all subjects
- Total DB or OL zavegepant exposure (patient-years), derived by summing (DB or OL zavegepant end date – DB or OL zavegepant start date + 1)/365.25 across all subjects.

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6.2.6.2 Measurements of Treatment Compliance

DB Treatment Compliance

DB treatment compliance categories are defined as follows for relevant protocol deviations (see Sections 6.2.4.1 and 9.1):

- DB study drug taken but not randomized
- DB capsule count compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL zavegepant start. Capsule count compliance is derived as 100 × actual cumulative DB capsule count/required cumulative DB capsule count, where
  - Actual cumulative DB capsule count is derived by summing the {number of days × number of capsules taken per day} across records with complete study medication start date and valid DB wallet ID.
    - Number of days for a record is derived as imputed study medication end date – study medication start date + 1.
  - Required DB cumulative capsule count is derived as {DB maxdate – DB study drug start date + 1} × {required number of capsules per day}, where
    - DB maxdate is defined as the latest of the (1) scheduled Week 2, 4, 8, and 12/EOT visit dates, and (2) DB study drug end date. Scheduled visits are identified from visit labels from the Visit Date CRF, and therefore exclude those containing "unscheduled" in the visit label.
    - If DB maxdate ≥ OL zavegepant start date, then DB maxdate is set to OL zavegepant start date – 1 day.
    - The required number of capsules per day is 4 for subjects in the zavegepant 100 mg or matching placebo group, and 8 for subjects in the zavegepant 200 mg or matching placebo group.
- More than the required number of DB capsules per day taken on any 1 day. This is determined from either of the following:
  - Records with complete study medication start date, valid DB wallet ID, and number of capsules taken per day > required number of capsules per day.
  - Overlapping records with valid DB wallet ID (see Section 9.4).
- Incorrect DB study drug taken
  - All the time. Defined as as-treated treatment group not equal to as-randomized treatment group, i.e., either of the following:
    - Subjects randomized to zavegepant who took (1) ≥ 1 capsule from a DB placebo wallet, and (2) no capsules from a DB zavegepant wallet
    - Subjects randomized to placebo who took (1) ≥ 1 capsule from a DB zavegepant wallet, and (2) no capsules from a DB placebo wallet.

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- At least once. Defined as (1) subjects randomized to zavegepant who took ≥ 1 capsule from a DB placebo wallet, or (2) subjects randomized to placebo who took ≥ 1 capsule from a DB zavegepant wallet.

OL Zavegepant Treatment Compliance

OL zavegepant treatment compliance categories are defined as follows for relevant protocol deviations (see Sections 6.2.4.1 and 9.1):

- OL zavegepant capsule count compliance < 80% from OL zavegepant start to later of last scheduled OLE Phase visit or OL zavegepant end. Capsule count compliance is derived as 100 × actual cumulative OL zavegepant capsule count/required cumulative OL zavegepant capsule count, where
  - Actual cumulative OL zavegepant capsule count is derived by summing the {number of days × number of capsules taken per day} across records with complete study medication start date and valid OL wallet ID.
  - Required cumulative OL zavegepant capsule count is derived as {OL maxdate – OL zavegepant start date + 1} where
    - OL maxdate is defined as the latest of the (1) scheduled Weeks 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64/EOT visit dates, and (2) OL zavegepant end date. Scheduled visits are identified from visit labels from the Visit Date CRF, and therefore exclude those containing "unscheduled" in the visit label.
    - The required number of capsules per day is based on the DB treatment group; see "DB Treatment Compliance".
- > 1 OL zavegepant capsule taken on any 1 day. This is determined from either of the following:
  - Records with complete study medication start date, valid OL wallet ID, and number of capsules taken per day > required number of capsules per day.
  - Overlapping records with valid OL wallet ID (see Section 9.4).
- OL zavegepant start date before DB study drug end date. Defined as OL zavegepant study drug start date ≤ DB study drug end date.
- OL zavegepant taken but DB study drug never taken. Defined as nonmissing OL zavegepant start date and missing DB study drug start date.

eDiary Usage Compliance

eDiary DBT usage compliance is derived as follows for relevant protocol deviations (see Sections 6.2.4.1 and 9.1):

- DB study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL zavegepant start: 100 × (total number of efficacy data days from the DB study drug start date to DB maxdate)/(total number of days from the DB study drug start date to the DB maxdate), where DB maxdate is defined previously.

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6.2.6.3 Nonstudy Concomitant Medications

Imputed medication start and end dates are used to assign non-study medication type (previous, current, DBT concomitant, OL zavegepant concomitant, or follow-up) to all non-study medications. Refer to the Core SAP for definitions of nonstudy medication types, non-study medication counting rules in frequency tables, non-study medication start and end date imputation, and TLF contents.

The by-subject listing of nonstudy medications is provided by therapeutic class and preferred name for the enrolled analysis set. Acute migraine and prophylactic migraine medications are identified, as well as medication type.

The following conventions apply to nonstudy medications:

- Nonstudy medications are identified from those reported on the Concomitant Medication CRF.
- Prophylactic migraine medications are defined as those with an indication of "prophylactic migraine medication" on the Concomitant Medications CRF.
- Acute migraine medications are defined as non-study medications with either (1) an indication of "acute migraine medication" from the Concomitant Medications CRF, or (2) preferred name containing triptan, ergotamine, lasmiditan, ubrogepant.

Nonstudy DBT Concomitant Medications

Frequency tables of the following nonstudy DBT concomitant medications are provided by treatment group, zavegepant pooled, and placebo pooled for the DBT safety analysis set: all; acute migraine; prophylactic migraine. Medications are displayed in descending order of zavegepant 200 mg frequency within therapeutic class and preferred name.

Nonstudy OL Zavegepant Concomitant Medications

A frequency table of the nonstudy OL zavegepant concomitant medications is provided by OL zavegepant dose and overall for the OL zavegepant safety analysis set. Medications are displayed in descending order of overall frequency within therapeutic class and preferred name.

6.3 Efficacy

Efficacy endpoints are assessed by as-randomized treatment group.

Randomization is stratified using IWRS, but the randomization strata used in analyses are based on actual data. The rationale for using the actual data in analyses is that sites may erroneously report the wrong stratum in IWRS. Hence, treatment group comparisons of continuous efficacy endpoints are *adjusted* by the randomization stratum, whereas treatment group comparisons of binary efficacy endpoints are *stratified* by the randomization stratum (except in subgroup analyses). If there are sparse data within a stratum, then results may be presented unstratified.

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

See Sections 7.2 and 7.3 for the definition of efficacy analysis periods and study days.

The by-subject listing of primary and secondary efficacy endpoints is provided for the full analysis set, and includes the reason for exclusion from the migraine analysis set: randomized more than once; not treated with study drug; treated with study drug and < 14 days of eDiary efficacy data in the OP; treated with study drug and < 14 days of eDiary efficacy data in all 3 months of the DBT Phase. Results for continuous endpoints are based on observed data, whereas results for binary endpoints incorporate missing data imputation. Subjects with ≥ 14 days of efficacy data (not necessarily consecutive) in the month defining the endpoint are flagged for secondary endpoints based on a single month.

6.3.1 Primary Efficacy Endpoint

Subjects are instructed to report headache occurrence, headache pain features and associated symptoms, aura occurrence, and medication used to treat headache or aura in the eDiary headache report every day in the OP and DBT Phase.

Migraine days per month are assessed as "migraine days per 4 weeks" to correspond with the 4-week visit schedule. Migraine days per month are based on 4-week intervals, and are prorated to account for missing migraine reports.

See Section 9.2.2 for the definition of eDiary efficacy data days, and Section 9.2.5 for the definition of migraine days.

The number of migraine days per month in the DBT Phase is examined relative to the number of migraine days per month in the OP for the migraine analysis set, i.e., subjects with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP analysis period and ≥ 1 month (i.e., 4-week interval) in the on-DBT efficacy analysis period.

Months in the DBT Phase are defined as follows:

- Month 1: ≤ 4 weeks; study days 1 to 28
- Month 2: > 4 to ≤ 8 weeks; study days 29 to 56
- Month 3: > 8 to ≤ 12 weeks; study days 57 to 84.

Analyses are based on eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods.

The number of migraine days per month is prorated to 28 days and derived as follows:

- OP: 28 × (total number of migraine days in the OP analysis period)/(total number of eDiary efficacy data days in the OP analysis period). Subjects must have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the OP to be evaluable.

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- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of migraine days in the month)/(total number of eDiary efficacy data days in the month). Subjects must have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the specified month to be evaluable.
- Overall DBT: 28 × (total number of migraine days through Month 3 in the on-DBT efficacy analysis period)/(total number of eDiary efficacy data days through Month 3 in the on-DBT efficacy analysis period).

6.3.1.1 Missing Efficacy Data

The frequency table of missing efficacy data in the OP and DBT Phase is provided for the full analysis set, and displays the following categories:

- Included in the migraine analysis set: ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and ≥ 1 month (i.e., 4-week interval) of the DBT Phase
  - Month 1: ≤ 4 weeks *
  - Month 2: > 4 to ≤ 8 weeks *
  - Month 3: > 8 to ≤ 12 weeks *
- Excluded from the migraine analysis set
  - < 14 days of eDiary efficacy data in the OP
  - < 14 days of eDiary efficacy data in all 3 months of the DBT Phase.

In the categories marked with "*", subjects must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

6.3.1.2 Descriptive Analyses

The table of values and changes (both absolute and percent) from the OP in the number of migraine days per month in the DBT Phase is provided for the migraine analysis set, and summarizes parameters descriptively as continuous variables (including 2-sided normal 97.5% CIs for mean change) by treatment group and placebo pooled and by pain intensity in each month of the DBT Phase and overall DBT. Pain intensity categories are (1) total (mild, moderate, severe, or not reported) and (2) moderate or severe. The table also presents results by subgroup level for all efficacy subgroups of interest described in Section 4.3.

In the percent change analyses, subjects must have ≥ 1 migraine day (i.e., absolute not prorated) of appropriate pain intensity in the OP analysis period to be included.

6.3.1.3 Treatment Group Comparisons

Analyses are based on the migraine analysis set and total pain intensity, unless specified otherwise.

Main Analysis: Migraine Analysis Set

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The main analysis of the primary endpoint uses a linear mixed effects model with repeated measures and the following attributes:

- Variables: change from the OP in number of total migraine days per month as the dependent variable; number of total migraine days per month in the OP as a covariate; treatment group, randomization stratum, month (i.e., Months 1 to 3 of the DBT Phase), and the month-by-treatment group interaction as fixed effects.
- Covariance structure for repeated measures accounting for within-subject correlated errors: assumed to be homogeneous across treatment groups, and initially specified as unstructured. If the model fails to converge or cannot be fit with an unstructured covariance structure, then other covariance structures are specified in the following hierarchical order: Toeplitz (which has heterogenous variances and heterogenous correlations between elements); first-order autoregressive with heterogeneous variances; and first-order autoregressive with homogeneous variances.
- SE estimation method: Huber-White "sandwich" (refer to the Core SAP).

Note that Protocol Versions 1 to 6 erroneously specify to include subject as a random effect in the model.

The table displays the following model estimates:

- Least-squares mean (LSM) change from OP, SE, and 97.5% CI by month and overall DBT for each treatment group and placebo pooled
- Difference in LSM changes from OP between each zavegepant treatment group and placebo pooled (zavegepant$_i$ − placebo pooled; i = 100 and 200), SE, and 97.5% CI at each month and overall DBT. Results in the overall DBT support the primary objective, results in the last month support secondary objective #2, results in the first month support secondary objective #3, and results in the second month support exploratory objective #1.

See Section 9.3.1 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

The main analyses are repeated for moderate or severe pain intensity to support exploratory objective #1. All variables in the model are the same, except (1) change from the OP in number of moderate or severe migraine days per month is the dependent variable, and (2) number of moderate or severe migraine days per month in the OP is the covariate. The corresponding model table has the same format.

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Percentages of Subjects with Reduction in Number of Migraine Days per Month

Analyses are based on the migraine analysis set using eDiary efficacy data dates in the OP and on-DBT efficacy analysis periods (see Section 7.2).

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In analyses by months, subjects must (1) achieve the reduction criterion from OP in the number of migraine days per month in the specified month, (2) have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the specified month, and (3) have ≥ 1 migraine day (absolute not prorated) of appropriate pain intensity in the OP analysis period to be classified as responders in the specified month. Otherwise, subjects are classified as failures in the specified month.

In analyses of the overall DBT, subjects must (1) achieve the reduction criterion from OP in the number of migraine days in the overall DBT, and (2) have ≥ 1 migraine day (absolute not prorated) of appropriate pain intensity in the OP analysis period to be classified as responders. Otherwise, subjects are classified as failures.

Treatment Group Comparisons

For each pain intensity (total; moderate or severe), the percentages of subjects with ≥ 50% reduction in the number of migraine days per month are compared between each zavegepant treatment group and placebo pooled using Mantel-Haenszel risk estimation with stratification by randomization stratum (yes, no). Percentages are calculated against the number of subjects in the migraine analysis set.

The table displays the following statistics at each month of the DBT Phase and overall DBT by pain intensity:

- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI for each treatment group and placebo pooled
- Stratified percentage difference between each zavegepant treatment group and placebo pooled (zavegepant$_i$ – placebo pooled; i = 100 and 200), ASE, and 97.5% CI
- Response rate (i.e., "n/N" and percentage), ASE, and 97.5% CI by randomization stratum for each treatment group and placebo pooled
- Percentage difference between each zavegepant treatment group and placebo pooled (zavegepant$_i$ – placebo pooled; i = 100 and 200), ASE, and 97.5% CI by randomization stratum.

Results for the endpoint of ≥ 50% reduction of moderate or severe pain intensity in the overall DBT support secondary objective #1. Results for all other endpoints support exploratory objective #2.

Note that Protocol Versions 1 to 6 specify to compare treatment groups using a stratified Cochran-Mantel-Haenszel test, which would produce a chi-square statistic. However, this SAP specifies Mantel-Haenszel risk estimation, which is more appropriate given the estimand is based on a difference in percentages between groups.

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6.3.2.2 Acute Migraine-specific Medication Days per Month in the DBT Phase

During the DBT Phase, subjects may record taking triptan, ergotamine, and other medications to treat headache or aura yesterday in the eDiary headache report.

Acute migraine-specific medication days per month are assessed as "acute migraine-specific medication days per 4 weeks" to correspond with the 4-week visit schedule. Acute migraine-specific medication days per month are based on 4-week intervals, and are prorated to account for missing migraine reports. See Section 9.2.4 for the definition of acute migraine-specific medication days.

Analyses are based on the migraine analysis set using eDiary efficacy data dates in the on-DBT efficacy analysis period.

The number of acute migraine-specific medication days per month in the DBT Phase are prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of acute migraine-specific medication days in the month)/(total number of eDiary efficacy data days in the month). Subjects must have ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in the specified month to be evaluable.
- Overall DBT: 28 × (total number of acute migraine-specific medication days through Month 3 in the on-DBT efficacy analysis period)/(total number of eDiary efficacy data days through Month 3 in the on-DBT efficacy analysis period).

Descriptive Analyses

The table of the number of acute migraine-specific medication days per month in the DBT analysis period is provided, and summarizes the parameter descriptively as a continuous variable (including 2-sided normal 97.5% CIs for mean) by treatment group and placebo pooled in each month of the DBT Phase and overall DBT.

Treatment Group Comparisons

Treatment groups are compared using a linear mixed effects modelwith repeated measures and the following attributes:

- Variables: number of acute migraine-specific medication days per month as the dependent variable; treatment group, randomization stratum, month (i.e., Months 1 to 3 of the DBT Phase), and the month-by-treatment group interaction as fixed effects
- Repeated measures error structure: See Section 6.3.1.3
- SE estimation method: See Section 6.3.1.3.

The table displays the following model estimates:

- LSM, SE, and 97.5% CI by month and overall DBT for each treatment group and placebo pooled

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- Difference in LSMs between each zavegepant treatment group and placebo pooled (zavegepant$_i$ – placebo pooled; i = 100 and 200), SE, and 97.5% CI at each month and overall DBT. Results in the overall DBT support secondary objective #4, whereas results at other time points support exploratory objective #6.

See Section 9.3.1 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

6.3.2.3 Overall Summary of Primary and Secondary Endpoints in Hierarchical Testing

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

- Continuous endpoints involving change from OP or baseline
  - n (i.e., number of subjects in the analysis set), LSM change, and 97.5% CI for each zavegepant treatment group and placebo pooled
  - Difference in LSM changes between each zavegepant treatment group and placebo pooled, and 97.5% CI..

  This applies to the primary endpoint and the following secondary efficacy and outcomes research endpoints: mean change in number of migraine days per month in the last month of the DBT Phase (see main analysis in Section 6.3.1); mean change in number of migraine days per month in the first month of the DBT Phase (see main analysis in Section 6.3.1); MSQoL restrictive role domain score mean change from baseline at Week 12 (see Section 6.5.1); and MIDAS total score mean change from baseline at Week 12 (see Section 6.5.2).
- Continuous endpoints not involving change from OP or baseline
  - n, LSM, and 97.5% CI for each zavegepant treatment group and placebo pooled
  - Difference in LSMs between each zavegepant treatment group and placebo pooled, and 97.5% CI.

  This applies to the secondary efficacy endpoint of the mean number of acute migraine-specific medication days per month over the entire DBT Phase (see Section 6.3.2.2).
- Binary endpoints
  - Response rate (“n/N” and percentage) and 97.5% CI for each zavegepant treatment group and placebo pooled
  - Stratified percentage difference between each zavegepant treatment group and placebo pooled, and 97.5% CI.

  This applies to the secondary efficacy endpoint of percentage of subjects with ≥ 50% reduction in number of moderate or severe migraine days per month over the entire DBT Phase (see Section 6.3.2.1).

Endpoints are displayed in the order presented in Sections 3.2.1 and 3.2.2.

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6.3.3 Exploratory Efficacy Endpoints

6.3.3.1 Acute Migraine Medication Days per Month in the DBT Phase

Acute migraine medication days per month are assessed analogously to acute migraine-specific medication days per month (see Section 6.3.2.2).

An acute migraine medication day is defined in Section 9.2.3.

Analyses are based on the migraine analysis set with eDiary efficacy data dates in the on-DBT efficacy analysis period.

The number of acute migraine medication days per month in the DBT Phase are prorated to 28 days.

Descriptive Analyses
The table of the number of acute migraine medication days per month in the DBT analysis period is provided, and has the same format as the one in Section 6.3.2.2.

6.3.4 Pharmacokinetics

Sparse PK sampling is performed at Week 4 and 8 at predose and approximately 1 hour postdose. PK last meal/snack date/times, collection date/times, and last IP dosing date/times are based on the PK CRF. Plasma zavegepant concentrations and collection date/times are from the external source Syneos Health.

The by-subject listing of plasma zavegepant concentrations is provided for the DBT efficacy analysis set, which includes analysis visit, analysis time point, PK collection date/time, last IP dose collection date/time, last meal/snack date/time before and after the predose sample concentration, study days corresponding to aforementioned date/times, and concentration. BLQ values are displayed as “BLQ”. A footnote specifies the lower limit of quantification (LLOQ) of 0.04 ng/mL and the upper limit of quantification (ULOQ) of 50.00 ng/mL.

First, PK samples are slotted into analysis visit windows defined in Section 7.3 according to PK collection date. Next, PK samples are slotted into analysis time point windows within analysis visit windows according to PK collection date/time as follows:

- Predose: last PK sample with collection date/time before the last IP dose collection date/time
- 1 hour postdose: first PK sample with collection date/time after the last IP dose collection date/time.

CRF and external PK data are merged by PK collection date/time, where the external data take precedence.

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6.4 Safety

Safety parameters include the following: deaths; AEs; laboratory tests; vital signs; physical measurements; electrocardiograms (ECGs); and Columbia-Suicidality Severity Rating Scale (C-SSRS.

Tables of safety endpoints are provided according to safety analysis period and analysis set as follows:

- On-DBT for the DBT safety analysis set by treatment group, zavegepant pooled, and placebo pooled
- Post-DBT pre-OL zavegepant for the interim safety analysis set by treatment group, zavegepant pooled, placebo pooled, and overall
- On-OL zavegepant for the OL zavegepant safety analysis set by OL zavegepant dose and overall
- On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set by DB or OL zavegepant dose and overall
- Follow-up for the follow-up safety analysis set by treatment group/OL zavegepant status and overall.

Treatment group is as-treated according to Section 6.1.1.1.

Measurements are slotted into analysis periods and analysis visits using the following steps:

1) Measurements are slotted into the pretreatment, on-treatment safety, and follow-up safety analysis periods.
2) Measurements are slotted into analysis visits in the analysis periods listed in the previous step (see Table 5). This does not apply to AEs.
3) Measurements in the on-treatment safety analysis period are slotted further into the on-DBT, post-DBT pre-OL zavegepant, and on-OL zavegepant safety analysis periods.

Refer also to the Core SAP for details about measurement slotting. See Sections 6.2.5, 7.2 and 7.3 for definitions of baseline, analysis periods, and analysis visit windows, respectively.

6.4.1 Adverse Events

Refer to the Core SAP for the following: AE start and end date imputation; death date derivation; rules for counting and rounding in AE frequency tables; definitions of AEs related to study drug, and AEs of special interest; and TLF contents.

Frequency tables of AEs by SOC and PT display AEs in descending order of overall frequency within SOC and PT, unless otherwise specified.

The by-subject listing of AEs (i.e., non-SAEs and SAEs) is provided for the enrolled analysis set.

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6.4.1.1 Deaths

Deaths are identified from any of the following sources:

- AE CRF with any of the following: PT or reported term of "death"; outcome of fatal; "yes" response to any death-related question (e.g., "Did the AE result in death?"; "Is a death certificate available?"; "Is an autopsy report available?"); complete or partially complete death date
- DB Subject Status CRF with any of the following: death as reason for DBT Phase non-completion; death as reason for not continuing to the next phase (see Section 6.2.3.3)
- OLE Subject Status CRF with any of the following: death as reason for OLE Phase non-completion; death as reason for not continuing to the Follow-up Phase (see Section 6.2.3.4)
- Follow-up Subject Status CRF: death as reason for Follow-up Phase non-completion (see Section 6.2.3.5).

The by-subject listing of deaths is provided for the enrolled analysis set.

6.4.1.2 AE Overviews

An AE overview frequency table displays the following categories without SOC and PT: any AE; AE related to study drug; AE leading to study drug discontinuation; SAE; SAE related to study drug; medication-overuse headache AE; hepatic-related AE; hepatic-related AE leading to study drug discontinuation; potential drug abuse AE; cardiovascular AE; and suicidality AE.

AE overview frequency tables are produced for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- Post-DBT pre-OL zavegepant for the interim safety analysis set
- On-OL zavegepant for the OL zavegepant safety analysis set
- On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

6.4.1.3 On-DBT AEs

Frequency tables of on-DBT AEs are provided for the DBT safety analysis set by SOC and PT for the following endpoints:

- AEs by worst intensity (secondary objective #7)
- AEs related to study drug by worst intensity
- SAEs (secondary objective #7)
- AEs leading to study drug discontinuation
- Hepatic-related AEs (secondary objective #9)

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- Hepatic-related AEs leading to study drug discontinuation (secondary objective #9)
- Potential drug abuse AEs, displayed in alphabetical order by worst intensity and PT without SOC
- Cardiovascular AEs
- Suicidality AEs.

Frequency tables of AEs by SOC and PT display AEs in descending order of zavegepant pooled within SOC and PT, unless otherwise specified.

6.4.1.4 On-OL Zavegepant AEs

Frequency tables of on-OL zavegepant AEs are provided for the OL zavegepant safety analysis set by SOC and PT for the same endpoints listed in Section 6.4.1.3.

6.4.1.5 Follow-up AEs

Frequency tables of follow-up AEs are provided by SOC and PT for the follow-up safety analysis set for the following endpoints:

- AEs by worst intensity
- SAEs.

6.4.2 Laboratory Tests

Laboratory tests are analyzed using results from local laboratory tests reported on CRFs and the external central laboratories (i.e., Cerba Research and ACM Global Laboratories). Central laboratories report both laboratory collection date and time, whereas CRFs capture only laboratory collection date.

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

- Hematology: Screening; Pre-randomization; Weeks 4, 12, 16, 24, 48, and 64; and early termination
- Serum chemistry: Screening; Pre-randomization; Weeks 4, 12, 16, 24, 48, and 64; and early termination. Exceptions are for the following:
  - LFTs (ALT, AST, ALP, TBL, direct bilirubin, indirect bilirubin): All visits except Baseline
  - Lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides) and HBA1c: Screening; Weeks 12 and 64; and early termination
- Urinalysis: Screening; Weeks 12 and 64; and early termination.

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

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- Laboratory test results (SI units). The listing displays all test results over time for subjects with select findings (grade 3 to 4 laboratory test abnormalities or positive pregnancy tests) at any time point.
- LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) for 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.

Refer to the Core SAP for laboratory tests of clinical interest for analyses (including identification of those with toxicity grades) and TLF contents.

6.4.2.1 Laboratory Test Abnormalities

Frequency tables of the worst (highest) laboratory test abnormality for each graded laboratory test are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL zavegepant for the OL zavegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Grade 3 to 4 results support other secondary objective #7.

6.4.2.2 LFT Elevations

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

Frequency tables of LFT elevations are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL zavegepant for the OL zavegepant safety analysis set
- On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Results support secondary objective #8 and exploratory objectives #8 and #9.

A confidence level of 97.5% is used for CIs.

LFT Plots

By-subject longitudinal LFT plots are provided for the safety analysis set with select LFT elevations in any safety analysis period. Study weeks are defined as study day/7, where study day is derived from the laboratory test collection date (see Section 7.3). Each figure also displays DB study drug and OL zavegepant dosing days using symbols along the x-axis (see Section 9.4), and denotes additional study milestones (e.g., start of the on-DBT safety analysis period, start of the OL zavegepant safety analysis period, and start of the follow-up safety analysis period) using vertical lines with their corresponding descriptions in footnotes.

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6.4.2.3 Laboratory Test Changes from Baseline over Time

The table of values and changes from baseline in hematology and serum chemistry laboratory tests is provided by treatment group, zavegepant pooled, placebo pooled, and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period; each scheduled visit from Week 14 through Week 64 and EOT in the on-OL zavegepant safety analysis period; and each scheduled visit in the follow-up safety analysis period. Results for zavegepant pooled and placebo pooled are displayed only at baseline and time points in the on-DBT safety analysis period. Results for overall are displayed only at baseline and time points in the on-OL zavegepant and follow-up safety analysis periods.

Note that scheduled visits vary according to laboratory test.

Refer to the Core SAP for (1) handling multiple values in an analysis visit window or on the same laboratory collection date, and (2) deriving the EOT value in an on-treatment safety analysis period. Note that Cerba Research provides sample code (vial/tube identifier), whereas ACM Global Laboratories provide accession identifier.

6.4.3 Vital Signs and Physical Measurements

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate. Physical measurements include height, weight, and body mass index (BMI). These parameters are measured with both measurement date and time at early termination and all visits except Weeks 2 and 14; height is measured at Screening only.

Refer to the Core SAP for TLF contents.

6.4.3.1 Vital Sign and Physical Measurement Changes from Baseline over Time

The table of values and changes from baseline in vital signs and physical measurements is provided by treatment group, zavegepant pooled, placebo pooled, and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period; each scheduled visit from Week 14 through Week 64 and EOT in the on-OL zavegepant safety analysis period; each scheduled visit in the follow-up safety analysis period. Results for zavegepant pooled and placebo pooled are displayed at baseline and time points in the on-DBT safety analysis period. Results for overall are displayed only at baseline and time points in the on-OL zavegepant and follow-up safety analysis periods.

Refer to the Core SAP for (1) handling multiple values in an analysis visit window or on the same measurement date, and (2) deriving the EOT value in an on-treatment safety analysis period.

6.4.3.2 Vital Sign and Physical Measurement Abnormalities

Frequency tables of vital sign and physical measurement abnormalities are provided for the following safety analysis periods and analysis sets:

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- On-DBT for the DBT safety analysis set
- On-OL zavegepant for the OL zavegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

6.4.4 Electrocardiograms

ECG parameters include RR, QRS, PR, QT, QTcB, QTcF, and ventricular heart rate. ECGs are measured with both acquisition date and time at the following visits: Screening; Weeks 4, 12, 16, 24, 48, and 64; and early termination. ECGs are analyzed using results from local tests reported on ECG CRFs and the external central vendor Bioclinica. Note that the ECG CRF collects RR in sec, not msec.

Refer to the Core SAP for TLF contents.

6.4.4.1 ECG Changes from Baseline over Time

The table of values and changes from baseline in ECG parameters is provided by DB treatment group, zavegepant pooled, placebo pooled, and overall for the safety analysis set at the following time points: baseline; each scheduled visit through Week 12 and EOT in the on-DBT safety analysis period; and each scheduled visit from Week 16 through Week 64 and EOT in the on-OL zavegepant safety analysis period. Results for zavegepant pooled and placebo pooled are displayed only at baseline and time points in the on-DBT safety analysis period. Results for overall are displayed only at baseline and time points in the on-OL zavegepant safety analysis period.

Refer to the Core SAP for (1) handling multiple values in an analysis visit window, and (2) deriving the EOT value in an on-treatment safety analysis period.

If there are multiple values on the same measurement date, then the following hierarchy is used to further break ties as available:

- Last central value collected timewise with the last ECG reference identifier
- Last local value collected timewise with the last entry date/time.

6.4.4.2 ECG Abnormalities

Frequency tables of ECG abnormalities are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL zavegepant for the OL zavegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

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

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6.4.5 C-SSRS

The C-SSRS is a clinician administered questionnaire used to help immediate risk of suicide. The C-SSRS is administered at early termination and all visits except the Pre-randomization Laboratory Visit. At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit.

Frequency tables of C-SSRS suicidality are provided for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set
- On-OL zavegepant for the OL zavegepant safety analysis set
- Follow-up for the follow-up safety analysis set.

Refer to the Core SAP for calculation of C-SSRS parameters and TLF contents.

6.4.6 Safety Narrative Subject Identifiers

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

- Death in any safety analysis period for the enrolled analysis set
- SAE during any of the following safety analysis periods and analysis sets:
  - On-DB or OL zavegepant for the DB or OL zavegepant safety analysis set
  - Follow-up for the DB or OL zavegepant safety analysis set
- Non-SAE leading to study drug discontinuation in any safety analysis period for the DB or OL zavegepant safety analysis set
- Event of special interest on DB or OL zavegepant for the DB or OL zavegepant safety analysis set:
  - ALT or AST > 3x ULN
  - ALT or AST > 3x ULN concurrent with TBL > 2x ULN
  - ALP or TBL > 2x ULN
  - Select hepatic-related non-SAE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
  - Cardiovascular non-SAE
  - Suicidality non-SAE.

Refer to the Core SAP for additional details.

6.5 Outcomes Research

Analyses are based on as-randomized treatment group for the DBT efficacy analysis set.

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Randomization strata used in analyses are based on actual data.

Outcomes research questionnaires and rating scales are MSQoL and MIDAS. These are assessed at Baseline, Week 12, Week 24, Week 64, and early termination. MSQoL and MIDAS are collected from respective CRFs with an assessment date.

Measurements are slotted into analysis periods and analysis visits using the following steps:

1) Measurements are slotted into the pretreatment, DBT outcomes research, and OL zavegepant outcomes research analysis periods.
2) Measurements are slotted into analysis visits in the analysis periods listed in the previous step (see Table 5).

See Sections 6.2.5, 7.2 and 7.3 for definitions of baseline, outcomes research analysis periods, and analysis visit windows, respectively.

A confidence level of 97.5% is used for CIs.

The by-subject listing of MSQoL and MIDAS is provided for the enrolled analysis set, and displays values and changes from baseline in MSQoL domain scores and MIDAS total, absenteeism, and presenteeism scores.

Refer to the Core SAP for the following: detailed descriptions of these questionnaires; calculating scores and imputing missing data; deriving categories; handling multiple questionnaires values in an analysis visit window or on the same assessment date; and TLF contents.

6.5.1 MSQoL

The MSQoL consists of 14 items across the following 3 domains: (1) restrictive role function, (2) preventative role function and (3) emotional function.

Refer to the Core SAP for calculating domain scores and imputing missing data.

Descriptive Analyses

The table of values and changes from baseline in scores are provided for each domain by treatment group, placebo pooled, and overall for the DBT efficacy analysis set at the following time points: baseline; Week 12 in the DBT outcomes research analysis period; Week 24 and Week 64 in the OL zavegepant outcomes research analysis period. Results for placebo pooled are displayed only at baseline and time points in the DBT outcomes research analysis period. Results for overall are displayed only at baseline and time points during the OL zavegepant outcomes research analysis period.

The frequency table of MSQoL domain score increase from baseline categories is provided by treatment group and overall for the DBT efficacy analysis set at the following time points: Week 12 in the DBT outcomes research analysis period; Week 24 and Week 64 in the OL zavegepant outcomes research analysis period. Results for placebo pooled are displayed only at baseline and

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time points in the DBT outcomes research analysis period. Results for overall are displayed only at baseline and time points during the OL zavegepant outcomes research analysis period.

Results support exploratory objective #12.

Treatment Group Comparisons

Analysis of the restrictive role function domain is based on the DBT efficacy analysis set with paired data, i.e., restrictive role function domain scores at both baseline and Week 12 of the DBT outcomes research analysis period.

Treatment groups are compared using a linear regression model with the following attributes:

- Variables: Week 12 change from baseline in the score as the dependent variable; baseline score as a covariate; treatment group and randomization stratum as fixed effects.
- SE estimation method: See Section 6.3.1.3.

The table provides n (i.e., number of subjects with paired data) and the following model estimates:

- LSM change from baseline at Week 12, SE, and 97.5% CI for each treatment group and placebo pooled
- Difference in LSM changes from baseline at Week 12 between each zavegepant treatment group and placebo pooled (zavegepant$_i$ – placebo pooled; i = 100 and 200), SE, and 97.5% CI.

Results support secondary objective #5.

See Section 9.3.2 for example SAS code. Model estimates by randomization stratum (yes, no) are presented in the same table, using additional models that exclude randomization stratum as a fixed effect.

6.5.2 MIDAS

The MIDAS is a retrospective, patient-administered, 5-item questionnaire that measures headache-related disability as lost time due to headache from paid work or school, household work, and non-work activities.

Refer to the Core SAP for calculating MIDAS scores (i.e., total, absenteeism, presenteeism, item) and imputing missing data.

Descriptive Analyses

The table of values and changes from baseline in total, absenteeism, presenteeism, and item scores is provided, and has a similar format as the one described in Section 6.5.1.

Results support exploratory objective #12.

Treatment Group Comparisons

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Analysis of the total score is based on the DBT efficacy analysis set with total scores at both baseline and Week 12 of the DBT outcomes research analysis period.

Treatment groups are compared using a linear regression model with the same attributes as the one described in Section 6.5.1. The table has the same format.

Results support secondary objective #6.

7 CONVENTIONS

7.1 Derived Dates

Derived dates are defined as follows:

- eDiary measurement date: Complete datepart{eDiary finding date/time} – 1 day, if from the eDiary headache log; complete datepart{eDiary finding date/time} otherwise
- eDiary efficacy data date: eDiary measurement date from the eDiary headache log
- Study drug start date: Earliest complete study medication start date from IP Dosing CRF records with number of capsules taken > 0. This is an analysis period reference date.
- Imputed study medication end date: If the study medication end date is (1) non-complete or (2) complete but before the study medication start date, then the imputed end date is set to the study medication start date. Otherwise, the imputed end date is set to the complete study medication end date. Derived only for IP Dosing CRF records with complete study medication start date and number of capsules taken > 0.
- Study drug end date: Latest of (1) complete study medication start dates, or (2) complete study medication end dates from IP Dosing CRF records with number of capsules taken > 0
- Study drug last date:
  - Before the final database lock: Study drug end date derived only for subjects who have either (1) or (2):
    - (1) "Yes" or "no" response to the phase completion question on the DB Subject Status CRF, and {either (1a) "no" response to the continuing to the Follow-up Phase question on the DB Subject Status CRF, or (1b) "no" response to the continuing to the next phase question on the DB Subject Status CRF, or (1c) "Follow-up" specified as the next phase on the DB Subject Status CRF}, and missing OL zavegepant start date
    - (2) "Yes" or "no" response to the phase completion question on the OLE Subject Status or Follow-up Subject Status CRF
  - Final database lock: Study drug end date

  This is an analysis period reference date.
- DB study drug start date: Earliest complete study medication start date from IP Dosing CRF records with number of capsules taken > 0 and valid DB wallet ID. This is an analysis period reference date.

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- DB study drug end date: Latest of (1) complete study medication start date, or (2) complete study medication end date from IP Dosing CRF records with number of capsules taken > 0 and valid DB wallet ID
- DB study drug last date:
  - Before the CSR database lock: DB study drug end date derived only for subjects with "yes" or "no" response to the phase completion question on the DB Subject Status, OLE Subject Status, or Follow-up Subject Status CRF
  - CSR database lock or after: DB study drug end date

  This is an analysis period reference date.
- OL zavegepant start date: Earliest complete study medication start date from IP Dosing CRF records with number of capsules taken > 0 and valid OL wallet ID. This is an analysis period reference date.
- OL zavegepant end date: Latest of (1) complete study medication start date, or (2) complete study medication end date from IP Dosing CRF records with number of capsules taken > 0 and valid OL wallet ID
- OL zavegepant last date:
  - Before the final database lock: OL zavegepant end date derived only for subjects with "yes" or "no" response to the phase completion question on the OLE Subject Status or Follow-up Subject Status CRF
  - Final database lock: OL zavegepant end date

  This is an analysis period reference date.
- DB or OL zavegepant start date: Study drug start date for subjects whose as-treated DB treatment group is zavegepant; OL zavegepant start date for subjects whose as-treated DB treatment group is placebo. This is an analysis period reference date.
- DB or OL zavegepant end date: Study drug end date for subjects whose as-treated DB treatment group is zavegepant; OL zavegepant end date for subjects whose as-treated DB treatment group is placebo
- DB or OL zavegepant last date: Study drug last date for subjects whose as-treated DB treatment group is zavegepant; OL zavegepant last date for subjects whose as-treated DB treatment group is placebo. This is an analysis period reference date.
- OP start date: Earliest of the following: screening visit date – 1 day; eDiary efficacy data date. The screening visit date is determined from the visit label from the Visit Date CRF. This is an analysis period reference date.
- OP end date:
  - If the study drug start date is not missing: study drug start date – 1 day
  - If the study drug start date is missing and the randomization date is not missing: randomization date – 1 day

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- If both study drug start date and randomization date are missing: Last contact date

This is an analysis period reference date.

- Last contact date:
  1. Earliest complete death date from the AE CRF, if it exists.
  2. Otherwise, the latest complete date of the following: AE start or end; ECG; eDiary finding; informed consent; IWRS randomization; laboratory test collection; non-study medication start or end; physical exam; physical measurement; procedure; rating scale; questionnaire; study medication start or end; vital sign; visit.
  3. 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: refer to the Core SAP.

No imputations are performed on these derived dates, unless specified otherwise.

Refer to the Core SAP for the definition of complete dates.

7.2 Analysis Periods

Measurements are slotted into analysis periods based on comparing measurement dates to analysis period reference dates (time is not applicable).

Analysis periods are defined as follows:

- eDiary efficacy endpoints (migraine days, acute migraine-specific medication days, acute migraine medication days)
  - OP: eDiary efficacy data date on or after the OP start date through the OP end date. Note that this is a subset of the pretreatment analysis period.
  - 28-day OP: eDiary efficacy data date on or after the OP start date through the earlier of {OP start date + 27 days; OP end date}. Note that this is a subset of the OP analysis period, and is used only to assess efficacy data issues during the OP as relevant protocol deviations.
  - On-DBT efficacy:
    - If the DB study drug last date or OL zavegepant start date is not missing: eDiary efficacy data date on or after the DB study drug start date through the earlier of the DB study drug last date and {OL zavegepant start date – 1 day}
    - If the DB study drug last date and OL zavegepant start date are both missing: eDiary efficacy data date on or after the DB study drug start date

    This period is used to assess efficacy during the DBT Phase.
- Pretreatment characteristics and safety endpoints *
  - Pretreatment: This period is abbreviated as “PRETRT” in listings, and is used to derive baseline values.

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- On-DBT safety: This period is abbreviated as "DBT" in safety listings, and is used to assess safety endpoints on DBT for the DBT safety analysis set.
- Post-DBT pre-OL zavegepant safety: This period is abbreviated as "INT" in safety listings, and is used to assess safety endpoints during the interim period (i.e., post-DBT pre-OL zavegepant) for the interim safety analysis set.
- On-OL zavegepant safety: This period is abbreviated as "OLZAV" in safety listings, and is used to assess safety endpoints for the OL zavegepant safety analysis set.
- On-DB or OL zavegepant safety: This period is used to assess safety endpoints on DB or OL zavegepant treatment for the DB or OL zavegepant safety analysis set.
- On-treatment safety: This period is used to derive analysis visit windows for slotting measurements, and may also be used to assess safety endpoints in a blinded integrated safety report, as needed.
- Follow-up safety: This period is abbreviated as "FU" in safety listings, and is used to assess safety endpoints during follow-up.

- Outcomes research endpoints (MSQoL, MIDAS,) *
  - DBT outcomes research: This period is abbreviated as "DBT" in outcomes research listings, and used to assess outcomes research endpoints during the DBT Phase.
  - OL zavegepant outcomes research: This period is abbreviated as "OLZAV" in outcomes research listings, and used to assess outcomes research endpoints during the OLE Phase.

For endpoints marked with "*", refer to the Core SAP for the definitions of analysis periods in Phase 2/3/4 multiple-dose studies with both DBT and OLE Phases. See Section 7.1 for derived dates for determining analysis periods.

7.3 Analysis Visit Windows

Refer to BHV3500-302 Protocol Section 4.3 (Table 1) for the schedule of assessments.

Refer to the Core SAP for defining randomization days, study days, zavegepant study days, and follow-up days in Phase 2/3/4 multiple-dose studies with both DBT and OLE Phases.

Analysis visit windows are shown in Table 5.

Table 5 Analysis Visit Windows

Analysis Period **Analysis Visit**	**Abbreviation in Listings**	**Analysis Day** **Analysis Visit Window**	**Target Day**
Pretreatment	**PRETRT**	**Randomization Day**	
Screening *		≤ -7 or missing	
Pre-randomization *	Prerand	-6 to -1	
Baseline *	Baseline	1	
Post-randomization @	Postrand	≥ 2	

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Analysis Period **Analysis Visit**	**Abbreviation in Listings**	**Analysis Day** **Analysis Visit Window**	**Target Day**
Outcomes Research /On-treatment Safety	**Outcomes Research: DBT or OLZAV/Safety: DBT, INT, OLZAV, or ONTRT**	**Study Day**	
Week 2		2 to 21	14
Week 4		22 to 42	28
Week 8		43 to 70	56
Week 12		71 to 91	85
Week 14		92 to 105	98
Week 16		106 to 126	112
Week 20		127 to 154	140
Week 24		155 to 182	168
Week 28		183 to 210	196
Week 32		211 to 238	224
Week 36		239 to 266	252
Week 40		267 to 294	280
Week 44		295 to 322	308
Week 48		323 to 350	336
Week 52		351 to 378	364
Week 56		379 to 406	392
Week 60		407 to 434	420
Week 64		435 to 462	448
Extension @	Ext	≥ 463	476
Follow-up Safety	**FU**	**Follow-up Day**	
Follow-up Week 2	FU Week 2	8 to 35	14
Follow-up Week 8	FU Week 8	36 to 77	56
Follow-up Extension @	FU Ext	≥ 78	84

***** For subjects in the enrolled analysis set excluded from the full analysis set, the visit label is used for slotting.
@ Denotes an extended visit in the analysis period and is displayed only in listings

Study days are used to define analysis visit windows in all analysis periods except follow-up safety. Follow-up days are used to define analysis visit windows in the follow-up safety analysis period.

8 CONTENTS OF REPORTS

All TLFs described in this SAP are produced for the LSLV final CSR (see Section 1.2).

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9 APPENDICES

9.1 Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- Previously treated with study drug in another multiple-dose BHV3500 study. Defined as subjects with (1) previous BHV3500 study subject identifiers from studies BHV3500-102/103/105/106/107/109/110/111/202 from the Demographics/Informed Consent CRF, and (2) who took ≥ 1 dose of study drug (e.g., zavegepant or placebo) in a multiple-dose study.
- Randomized or treated with study drug under > 1 subject identifier. These are identified from the Protocol Deviations CRF.
- Migraine history issue, defined as any of the following subcategories:
  - ≤ 3 moderate or severe migraine days per month in the 3 months prior to screening, if originally consented to Protocol Version 3 or lower
  - ≥ 19 moderate or severe migraine days per month in the 3 months prior to screening, if originally consented to Protocol Version 3 or lower
  - No history of chronic migraine, if originally consented to Protocol Version 4 or higher. Defined as having "no" or missing response to chronic migraine by history from the Migraine History CRF.
  - < 1 year between age at informed consent and age at chronic migraine onset, if originally consented to Protocol Version 4 or higher
  - ≤ 7 migraine days per month of any pain intensity in the 3 months prior to screening, if originally consented to Protocol Version 4 or higher
  - ≤ 14 headache days per month in the 3 months prior to screening, if originally consented to Protocol Version 4 or higher
  - No headache-free days per month in the 3 months prior to screening, if originally consented to Protocol Version 4 or higher.

  These are based on the Migraine History CRF.
- 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

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- Ischemic bowel disease
- Uncontrolled hypertension

These are identified from "yes" responses to having risk factors listed above on the Cardiac and Other Risk Factors CRF. Only subcategories with "yes" responses are presented.

- Medical history, defined as any of the following subcategories:
  - Basilar migraine or hemiplegic migraine
  - Chronic pain syndrome or other pain syndromes other than migraine present at screening
  - Dementia or significant neurological disorder other than migraine present at screening
  - Major depressive disorder with atypical antipsychotics taken as nonstudy prior medications, schizophrenia, bipolar disorder, or borderline personality disorder present at screening. PTs must contain any of the following: major depress; schizophrenia; bipolar disorder; borderline personality disorder. Refer to the Core SAP for atypical antipsychotics and nonstudy prior medications.
  - Gilbert's syndrome or any other active hepatic or biliary disorder present at screening
  - Gastric or small intestinal surgery

  For each subcategory, PTs are displayed alphabetically as additional subcategories. Unless specified otherwise, PTs are identified by the sponsor medical lead or designee from reviewing a list of unique medical history SOC and PTs. Active medical history status is also identified by the sponsor medical lead or designee from reviewing by-subject listings of medical history and AEs.

  Present at screening is defined as medical history end date of ongoing (refer to the Core SAP) or on or after the informed consent date.
- Finding out of range, defined any as any of the following subcategories:
  - Females with a positive pregnancy test on or after informed consent (see Section 6.4.2).
  - Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 mL/min/1.73m^2 during pretreatment *
  - BMI ≥ 33 kg/m^2 during pretreatment *
  - C-SSRS suicidal ideation with active intent or plan to act, or suicidal behavior present during pretreatment. Defined as having a "yes" response to any of the following C-SSRS questions during pretreatment:
    - Suicidal ideation question 4 (active suicidal ideation with some intent to act, without specific) or 5 (active suicidal ideation with specific plan and intent)
    - Suicidal behavior question 1 (actual attempt), 3 (interrupted attempt), 4 (aborted attempt), 5 (preparatory acts or behavior), or 6 (suicidal behavior).

  For the subcategories marked with "*", all nonmissing values during the pretreatment analysis period must meet the deviation criteria in order to be considered a deviation.

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- Efficacy data issue during the OP, defined as any of the following subcategories:
  - ≤ 5 migraine days, if originally consented to Protocol Version 3 or lower
  - ≤ 7 migraine days, if originally consented to Protocol Version 4 or higher
  - ≥ 19 headache days, if originally consented to Protocol Version 3 or lower
  - ≤ 14 headache days, if originally consented to Protocol Version 4 or higher
  - No headache-free days, if originally consented to Protocol Version 4 or higher. A headache-free day is defined as a day of eDiary efficacy data that is not a headache day of total pain intensity (see Section 9.2.6).
  - ≤ 23 days of eDiary efficacy data (see Section 9.2.2).

  These are assessed during the 28-day OP analysis period (see Section 7.2). Migraine days and headache days are absolute, not prorated to 28 days per month (see Sections 9.2.5 and 9.2.6), and of total pain intensity.

Protocol version for original consent is from the Inclusion/Exclusion CRF.

Relevant subject management protocol deviations include the following categories:

- Randomization stratum discrepancies between IWRS and actual 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 usage issue, defined as any of the following subcategories:
  - Prophylactic migraine medication started or stopped from 12 weeks before informed consent to randomization. Defined as informed consent date – 84 days ≤ imputed non-study medication start or end date ≤ IWRS randomization date.
  - > 1 prophylactic migraine medication taken on or after informed consent. "> 1" is defined as > 1 unique preferred name.
- DB study drug dosing issue, defined as any of the following subcategories (see Section 6.2.6.2):
  - DB study drug taken but not randomized
  - More than the required number of DB capsules taken on any 1 day
  - DB capsule count compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL zavegepant start
  - Incorrect DB study drug taken

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- OL zavegepant dosing issue, defined as any of the following subcategories (see Section 6.2.6.2):
  - OL zavegepant capsule count compliance < 80% from OL zavegepant start to later of last scheduled OLE Phase visit or OL zavegepant end
  - More than the required number of OL zavegepant capsules taken on any 1 day
  - OL zavegepant start before DB study drug end
  - OL zavegepant taken but DB study drug never taken
- eDiary usage compliance < 80% from DB study drug start to later of last scheduled DBT Phase visit or DB study drug end/OL zavegepant start (see Section 6.2.6.2)
- Prohibited non-study medications, defined as any of the following subcategories:
  - Atypical antipsychotics, divalproex, valproic acid, or valproate taken on or after informed consent #
  - Butterbur root or extract taken up to 14 days before randomization or afterward
  - Calcitonin gene-related peptide (CGRP) antagonist biologic or small molecule taken on or after informed consent #
  - Ergotamine taken on or after informed consent
  - Lamotrigine taken on or after informed consent
  - Narcotic (barbiturate or opioid) taken up to 2 days before randomization or afterward #

For the subcategories marked with "#", preferred names are displayed alphabetically as additional subcategories. Medications taken up to *X* days before a reference date or afterward are defined as those with imputed medication start date or imputed end date ≥ reference date – *X*. Refer to the Core SAP for additional details about prohibited non-study medications.

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.

9.2 eDiary Efficacy

9.2.1 Efficacy Parameters

On a given day, subjects use the eDiary to provide responses to the following efficacy parameters occurring yesterday:

- Headache (yes, no)
- If the response to headache is "yes", then responses to the following pain features and associated symptoms are collected:
  - Lasts at least 30 minutes (yes, no)
  - Pain intensity (mild, moderate, severe)
  - Unilateral (yes, no)

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- Pulsating (yes, no)
- Worsen or avoid physical activity (yes, no)
- Nausea (yes, no)
- Vomiting (yes, no)
- Photophobia (yes, no)
- Phonophobia (yes, no)

- Aura (yes, no)
- If the response to headache or aura is "yes", then the responses to the following parameters about taking medications to treat headache or aura are collected:
  - Triptan (yes, no)
  - Ergotamine (yes, no)
  - Other medication (yes, no).

These efficacy parameters are collected together as a set with the same eDiary finding date/time for a subject. It is expected that subjects have only 1 set of efficacy parameters collected on a given eDiary finding date. Handling of multiple sets on the same date are discussed in subsequent sections.

9.2.2 eDiary Efficacy Data Day

A day of eDiary efficacy data is defined as any complete eDiary efficacy data date (see Section 7.1).

9.2.3 Acute Migraine Medication Day

An acute migraine medication day is defined as either (1) or (2):

1) Acute migraine-specific medication day (see Section 9.2.4)

2) Migraine day (see Section 9.2.5) with a "yes" response to the question about taking other medications to treat headache or aura.

Thus, acute migraine medication days are a subset of migraine days (see Section 9.2.5). If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess acute migraine medication day status on that day, regardless of finding time. For example, if a subject has both "yes" and "no" responses to the question about taking triptan on that day, then the subject is considered to have taken acute migraine medication on that day.

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9.2.4 Acute Migraine-specific Medication Day

An acute migraine-specific medication day is defined as a day of eDiary efficacy data with a "yes" response to either of the 2 questions about taking triptan or ergotamine to treat headache or aura.

Thus, acute migraine-specific medication days are a subset of acute migraine medication days and migraine days (see Sections 9.2.3 and 9.2.5, respectively). If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess acute migraine-specific medication day status on that day, regardless of finding time.

9.2.5 Migraine Day

A migraine day is defined as a day of eDiary efficacy data with either (1) or (2):

1) Qualified migraine headache, defined as meeting both criteria a and b:
    a. Headache lasting ≥ 30 minutes: "Yes" response to the question about lasting ≥ 30 minutes
    b. Meeting ≥ 1 of the following criteria (i or ii):
        i. ≥ 2 of the following pain features:
            1. Unilateral: "Yes" response to the question about unilateral
            2. Pulsating: "Yes" response to the question about pulsating
            3. Moderate or severe pain intensity
            4. Worsen or avoid physical activity: "Yes" response to the question about worsen or avoid physical activity
        ii. ≥ 1 of the following associated symptoms:
            1. Nausea: "Yes" response to the question about nausea
            2. Vomiting: "Yes" response to the question about vomiting
            3. Both photophobia and phonophobia: "Yes" responses to the questions about photophobia and phonophobia
2) Acute migraine-specific medication day (see Section 9.2.4).

Migraine days are a subset of headache days (see Section 9.2.6).

If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess migraine day status on that day, regardless of finding time. Migraine pain intensity is set to the greatest pain intensity on that day.

9.2.6 Headache Day

A headache day is defined as a day of eDiary efficacy data with either (1), (2), or (3):

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1) Migraine day (see Section 9.2.5)
2) Headache that lasts ≥ 30 minutes: "Yes" response to the question about lasting ≥ 30 minutes
3) Headache of any duration for which acute headache treatment is administered: Meeting both of the following criteria (a and b):
   a) "Yes" response to the question about having a headache
   b) "Yes" response to any of the 3 questions about taking medications to treat headache or aura (i.e., triptan, ergotamine, or other medications).

If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively to assess headache day status on that day, regardless of finding time. Headache pain intensity is set to the greatest pain intensity on that day.

9.3 SAS Code

9.3.1 Linear Mixed Effects Model with Repeated Measures

Consider the following variables used to evaluate the primary efficacy endpoint using a linear mixed effects model with repeated measures:

- mdmchg: change from the OP in migraine days per month; continuous variable
- mdmop: migraine days per month during the OP; continuous variable
- month: month; categorical variable with levels of 1, 2, and 3
- rndstr: randomization stratum; categorical variable with levels of 1 and 2 to denote yes and no, respectively
- trt: treatment group; categorical variable with levels of 1, 2, 3, and 4 to denote zavegepant 100 mg, zavegepant 200 mg, placebo 100 mg, and placebo 200 mg, respectively
- usubjid: unique subject identifier; categorical variable.

Then the SAS code is as follows:

```
proc mixed alpha=0.025 empirical;
class usubjid rndstr trt month;
model mdmchg = mdmop rndstr trt month trt*month;
repeated month / subject=usubjid type=un; /* unstructured covariance */
lsmeans trt trt*month / alpha=0.025 cl diff;
lsmestimate trt 'placebo pooled overall DBT' 0 0 1 1,
                'zav100 vs placebo pooled overall DBT' 2 0 -1 -1,
                'zav200 vs placebo pooled overall DBT' 0 2 -1 -1 /
                divisor=2 alpha=0.025;
lsmestimate trt*month 'placebo pooled month 1' 0 0 0 0 0 0 1 0 0 1 0 0,
                      'placebo pooled month 2' 0 0 0 0 0 0 0 1 0 0 1 0,
                      'placebo pooled month 3' 0 0 0 0 0 0 0 0 1 0 0 1,
                      'zav100 vs placebo pooled month 1' 2 0 0 0 0 0 -1 0 0 -1 0 0,
```

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```
                    'zav100 vs placebo pooled month 2' 0 2 0 0 0 0 0 -1 0 0 -1 0,
                    'zav100 vs placebo pooled month 3' 0 0 2 0 0 0 0 0 -1 0 0 -1,
                    'zav200 vs placebo pooled month 1' 0 0 0 2 0 0 -1 0 0 -1 0 0,
                    'zav200 vs placebo pooled month 2' 0 0 0 0 2 0 0 -1 0 0 -1 0,
                    'zav200 vs placebo pooled month 3' 0 0 0 0 0 2 0 0 -1 0 0 -1 /
                    divisor=2 alpha=0.025;
run;
```

9.3.2 Linear Regression Model

Consider the following variables used to evaluate either of the 2 secondary outcomes research endpoints using a linear regression model:

- scorechg: score change from baseline at Week 12; continuous variable
- rndstr: randomization stratum; categorical variable with levels of 1 and 2 to denote yes and no, respectively
- scorebl: baseline score; continuous variable
- trt: treatment group; categorical variable with levels of 1, 2, 3, and 4 to denote zavegepant 100 mg, zavegepant 200 mg, placebo 100 mg, and placebo 200 mg, respectively
- usubjid: unique subject identifier; categorical variable.

Then the SAS code is as follows:

```
proc mixed alpha=0.025 empirical;
class usubjid rndstr trt;
model scorechg = scorebl rndstr trt ;
repeated / subject=usubjid;
lsmeans trt / alpha=0.025 cl diff;
lsmestimate trt 'placebo pooled overall DBT' 0 0 1 1,
                'zav100 vs placebo pooled overall DBT' 2 0 -1 -1,
                'zav200 vs placebo pooled overall DBT' 0 2 -1 -1 /
                divisor=2 alpha=0.025;
run;
```

9.4 Study Drug Dosing Day

A study drug dosing day is defined as a day on which ≥ 1 capsule of study drug was taken.

For each subject, study drug dosing days and the number of capsules per day are determined for every day in the interval defined from the study drug start date to the study drug end date inclusive.

First, study medication records with complete study medication start date, complete imputed study medication end date, and number of capsules taken per day > 0 are selected. Imputed study medication end date, study drug start date, and study drug end date are derived (see Section 7.1).

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Next, records are sorted by study medication start date, imputed study medication end date, wallet ID, and number of capsules taken per day.

Let [study medication start date1, imputed study medication end date1] and [study medication start date2, imputed study medication end date2] denote any 2 records.

Overlapping records are defined as those with maximum(study medication start date1; study medication start date2) ≤ minimum(imputed study medication end date1; imputed study medication end date2).

- All days from the maximum to the minimum inclusive are considered overlapping study drug dosing days on which the number of capsules taken per day > 1.
- The number of capsules taken per day is summed across overlapping study drug dosing days to determine whether it exceeds the required number of capsules per day (see Section 6.2.6.1).
- Note that overlapping records need not be consecutive.

Gaps between 2 consecutive records are defined as study medication start date2 – imputed study medication end date1 ≥ 2 days. All days from the imputed study drug end date1 + 1 day to the study medication start date2 – 1 day inclusive are considered days on which no study drug was taken (i.e., not study drug dosing days).

A DB study drug dosing day is defined as a day on which ≥ 1 capsule of DB study drug was taken. DB study drug dosing days are determined using valid DB wallet IDs.

An OL zavegepant dosing day is defined as a day on which ≥ 1 capsule of OL zavegepant study drug was taken. OL zavegepant dosing days are determined using valid OL wallet IDs.

Example:

Suppose study medication data are as follows for a given subject in the zavegepant 100 mg treatment group:

Study Medication Start Date	Study Medication End Date	Imputed Study Medication End Date	Number of Capsules Taken per Day	Note
01JAN2022	03JAN2022	03JAN2022	4	
04JAN2022	05JAN2022	05JAN2022	0	Excluded from analysis
06JAN2022	09JAN2022	09JAN2022	4	
09JAN2022	11JAN2022	11JAN2022	8	1-day overlap with previous record
13JAN2022		13JAN2022	4	1-day gap between previous record

Then study drug start date = 01JAN2022 and study drug end date = 13JAN2022.

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Study drug dosing days and number of capsules taken per day are derived as follows for the subject, taking overlaps and gaps into account:

Date	Number of Capsules per Day	Study Drug Dosing Day Flag
01JAN2022	4	Y
02JAN2022	4	Y
03JAN2022	4	Y
04JAN2022	0	
05JAN2022	0	
06JAN2022	4	Y
07JAN2022	4	Y
08JAN2022	4	Y
09JAN2022	12	Y
10JAN2022	8	Y
11JAN2022	8	Y
12JAN2022	0	
13JAN2022	4	Y

The subject has a total of 10 study drug dosing days and 56 capsules taken. There are 3 days on which the required number of capsules taken was exceeded.

10 REFERENCES

1. Reference-based MI via multivariate normal RM (the “five macros” and MIWithD) from the Drug Information Association scientific working group on estimands and missing data. London School of Hygiene and Tropical Medicine, 2021. at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data.)

2. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. Journal of Biopharmaceutical Statistics 2013;23:1352-71.

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