Statistical Analysis Plan for Interventional Studies

Text Only

Protocol Number: BHV-3500-204 (C5301005)

Protocol Title: A Phase 1b, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate Safety and Efficacy of Oral Zavegepant in Subjects with Mild Allergic Asthma

Protocol Version and Date: (DD-Mmm-YYYY): Version 3.0 22-Mar-2023

Syneos Health Project Code: 7019323

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	09-Aug-2021	PPD	First Draft
0.2	17-Sep-2021	PPD	Revisions per Biohaven's comments
0.3	20-Oct-2021	PPD	Revisions per Biohaven's comments
0.4	10-Dec-2021	PPD	Revisions per Biohaven's comments
0.5	22-Dec-2021	PPD	Revisions per Biohaven's comments
1.0	05-Jan-2022	PPD	Final version
1.1	02-Mar-2023	PPD	Amendement per Pfizer's comments for dry run
2.0	16-Jun-2023	PPD	Amendement per Pfizer's comments to reduce the TLFs and streamline the CSR.

I confirm that I have reviewed this document and agree with the content.

Approvals

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Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AHR	Allergen-induced Airway Hyperresponsiveness
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
ATC4	Anatomical Therapeutic Chemical Classification Level 4
AUC	Area Under the Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass index
CGRP	Calcitonin Gene-related Peptide
CI	Confidence Interval
CRF	Case Report Form
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variance
DAIDS	Division of Aids
EAR	Early Asthmatic Response
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web-based Response System
LAR	Late Asthmatic Response
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat

Abbreviation	Description
NCA	Non-compartmental Analysis
PK	Pharmacokinetic
PT	Preferred Term
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
S-STS	Sheehan Suicidality Tracking Scale
TFL	Table, Figure and Listing
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. This SAP is based on BHV3500-204 Protocol Version 3.0 (22Mar2023).

The Rimegepant (BHV3000)/Zavegepant (BHV3500) Core Statistical Analysis Plan (the "Core SAP") describes analysis details and methodologies common to the BHV3500 program and is incorporated by reference. The Core SAP assumes primacy for any matter where this SAP is silent (and the relevant content of the Core SAP could feasibly apply) or where the Core SAP is directly referenced as applicable. Otherwise, should any discrepancy exist between the Core SAP and this SAP, this SAP assumes primacy.

Note that the study was terminated prematurely in 1Q2023 due to low enrollment. Thus, the SAP is being amended from Version 1.1 to 2.0 to reduce the number of TLFs to streamline the CSR.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of database lock.

3. Study Objectives

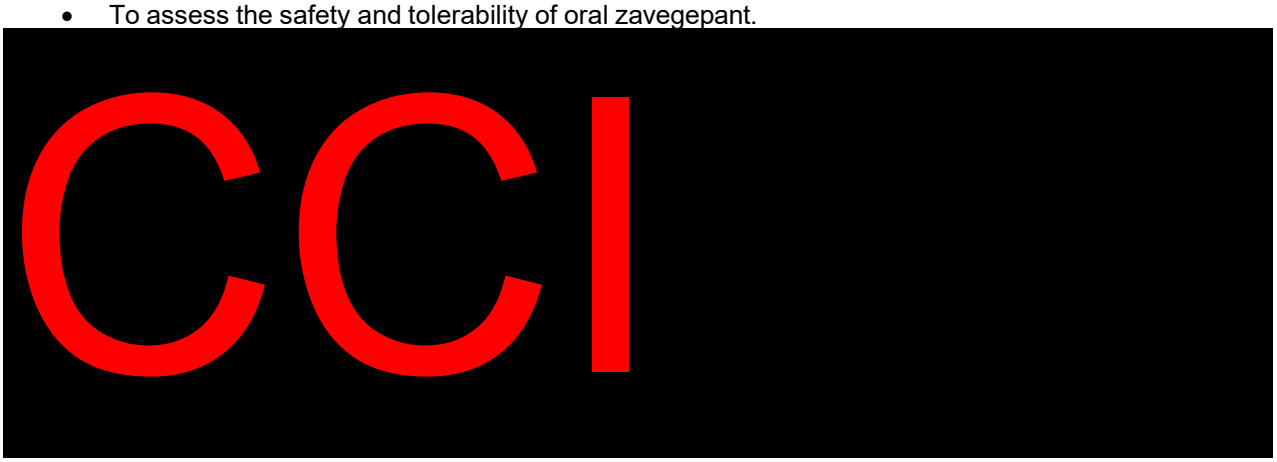
3.1. Primary Objective

The primary objective of this study is to evaluate the allergen-induced late asthmatic response (LAR) between subjects treated with zavegepant and placebo after 28 days of treatment.

3.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the allergen-induced early asthmatic response (EAR) between subjects treated with zavegepant and placebo.
- To evaluate the allergen-induced airway hyperresponsiveness (AHR) measured at 24 hours post-allergen challenge, between subjects treated with zavegepant and placebo.
- To assess the safety and tolerability of oral zavegepant.



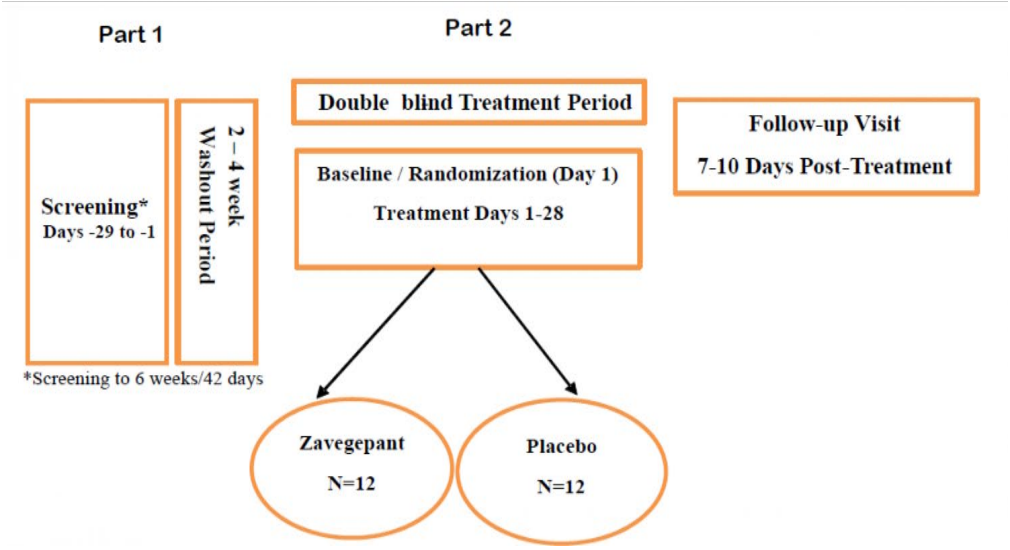
Study Details/Design

3.4. Brief Description

This is a multicenter, phase 1b, double-blind, parallel-group, randomized study of 24 subjects to evaluate the safety and efficacy of 150 mg oral zavegepant versus placebo twice daily for the treatment of allergen-induced asthma. Individuals with stable, mild allergic asthma, with a history of episodic wheeze and shortness of breath, will be eligible for enrollment. The study will be divided into 2 parts. Part 1 is the screening period of up to 28 days to obtain a cohort of subjects with documented EAR (defined as ≥20% fall in forced expiratory volume in 1 second (FEV_1) 0 to 2 hours after allergen challenge) and LAR (defined as ≥15% fall in FEV_1 3 to 7 hours after allergen challenge) to an inhaled incremental allergen challenge and AHR defined by methacholine PC_{20} ≤16 mg/mL by inhaled incremental methacholine challenge. Part 1 consists of Visits 1 through 4. Part 2 is the dosing period of approximately 28 days. Part 2 consists of Visits 5 through 9. Subjects will be randomized in a 1:1 ratio to receive 150 mg zavegepant or matching placebo to be taken twice daily. All subjects will undergo a 3-day allergen challenge triad, morning doses will be taken before any laboratory procedures and study treatment will end with their evening dose at the end of the challenge. A follow-up period consisting of an onsite visit will be conducted approximately 7 to 10 days after the last study treatment.

Figure 1 presents the general study schematic.

Figure 1. Study Schematic



3.5. Determination of Sample Size

This study will enroll 24 subjects, 12 per arm. The sample size was determined based on practical considerations, as well as statistical considerations. Assuming standard deviation (SD)=9, with N=24 subjects (12 per arm), at a 2-sided 5% alpha-level, the study will have more than 80% power to detect an absolute between treatment difference of 11 percentage points in the primary endpoint (maximum percentage decrease in the FEV_1 measured 3 to 7 hours after allergen challenge).

Table 1 presents the 95% confidence intervals (CIs) for observed differences between treatment in maximum percentage decrease in LAR FEV_1.

Table 1. CIs (95%) for Observed Differences Between Zavegepant and Placebo in Maximum Percentage Decrease in LAR FEV_1

Observed Absolute Difference in Maximum % Decrease in LAR FEV_1	2-sided 95% CI
9%	(1.4%, 16.6.%)
11%	(3.4%, 18.6%)
13%	(5.4%, 20.6%)

3.6. Treatment Assignment and Blinding

The investigator or designee will obtain a subject number and treatment assigned via an Interactive Web-based Response System (IWRS). The IWRS system will assign a subject specific blinded study treatment kit that will contain 8 wallets, enough for the total treatment duration, to be dispensed to subjects. Once the kits/wallets have been assigned, they cannot be dispensed to another study subject.

Once a subject completes the study, or if a subject is discontinued early from the study, the investigator or designee must access the IWRS to document discontinuation of the subject from study participation.

After the subject's treatment assignment number is obtained from the IWRS, the number will be provided to the investigator or designee at the study center who is responsible for distribution of study treatment. The IP and placebo will be identical in appearance and labeled in a blinded manner. No study site personnel, subject, Sponsor personnel, or Sponsor designee will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. If an investigator becomes unblinded to a given subject's study treatment, that subject will be discontinued from the study unless there are ethical reasons for the subject not to be discontinued; approval from the Sponsor's medical monitor must be obtained in such instances.

In the event that an emergency unblinding is required for a subject because of an adverse event (AE) or concerns for the subject's safety or well being, the investigator may break the randomization code for the subject via the IWRS. The investigator is responsible for notifying the medical monitor and/or Sponsor of such an event as soon as possible. The unblinding and its cause will also be documented in the electronic case report form (eCRF).

3.7. Administration of Study Medication

After subjects have met all eligibility requirements in Part 1 and completed the rest/washout period, they will be randomized in a 1:1 ratio to receive zavegepant or placebo. IP will be dispensed at Visit 5. Subjects will take 6 25-mg capsules twice daily, in the morning and evening, for at least 28 days. Subjects should dose consistently at the same time of day, preferably in the morning and evening. Each dose of study drug should be taken while fasting (e.g., at least 1 hour before breakfast/first meal of the day for the first dose, and at least 4 hours after the previous meal for the second dose). Subjects should not consume food other than water for 1 hour after dosing.

3.8. Study Procedures and Flowchart

The schedule of assessments is provided in Table 2 as below.

Table 2. Schedule of Assessments

	Part 1: Screening[a]				**2-4 Week Washout From Screening**	**Part 2: Dosing/Treatment**				**Follow-up**
Visit #	**1**	**2**	**3**	**4**		**5**	**6**	**7**	**8**	**9**
		3-Day Allergen Triad					**3-Day Allergen Triad**			
Day(s)	**-29 to -16**	**-15 (±3d)**	**-14 (±3d)**	**-13 (±3d)**		**1[b]**	**~26 (+ 3d)**	**~27 (+ 3d)**	**~28 (+ 3d)**	**~35 - 41**
Informed consent	X									
Inclusion/Exclusion criteria	X	X	X			X				
Demographics/ Medical history/medication history	X									
Vital signs	X					X	X	X	X	
Physical examination, including BMI[c]	X									X
Electrocardiogram	X									X
Spirometry	X	X	X	X		X	X	X	X	
Pregnancy test[d]	X					X			X	
Clinical laboratory tests (hematology, chemistry)	X					X			X	X
Urinalysis	X					X			X	
Urine drug testing	X									
Allergy skin (prick) test	X									
Methacholine challenge		X		X		X	X		X	
Sputum induction		X	X	X		X	X	X	X	
Allergen skin titration test[e]	X	X								
Allergen inhalation challenge			X					X		
Randomization and Dosing[f, g]						X	X	X	X	
Meal and Daily Study Drug Dosing Diary[h]						X	X	X	X	
Pharmacokinetic							X	X	X	

	Part 1: Screening[a]				2-4 Week Washout From Screening	Part 2: Dosing/Treatment				Follow-up
Visit #	**1**	**2**	**3**	**4**		**5**	**6**	**7**	**8**	**9**
		3-Day Allergen Triad					**3-Day Allergen Triad**			
Day(s)	**-29 to -16**	**-15 (±3d)**	**-14 (±3d)**	**-13 (±3d)**		**1[b]**	**~26 (+ 3d)**	**~27 (+ 3d)**	**~28 (+ 3d)**	**~35 - 41**
sampling[i]										
Ongoing and concomitant medications	X	X	X	X		X	X	X	X	X
Adverse events		X	X	X		X	X	X	X	X
S-STS	X					X			X	

Abbreviations: BMI=body mass index; d=day; ECG=electrocardiogram; FEV_1= forced expiratory volume in 1 second; h=hour(s); max=maximum; min=minimum; PC_{20}=provocation concentration causing a 20% decline in FEV_1; SABA= short-acting beta-agonists; S-STS=Sheehan-Suicidality Rating Scale; WOCBP=women of childbearing potential.

a **Part 1**: All screening procedures will be completed and results returned within Days -29 to Day -13.
b **Part 2/Day 1**: Subjects will be confirmed as recovered on Day 1 (e.g., confirmation of hyperresponsiveness recovery of methacholine PC_{20} not more than 1 doubling dose lower than baseline; return to FEV_1 within 90% of baseline) prior to initiation of dosing.
c A full examination will be performed at screening and at follow-up. BMI will be calculated at Screening Visit 1.
d Serum pregnancy test conducted at screening; urine pregnancy testing at all other visits as indicated. Results of the pregnancy test are required before dosing. Source documents should document that WOCBP agree to use 2 effective forms of contraception and men with WOCBP partners agree to use condoms with a spermicide during treatment.
e Allergen skin titration test can be performed at either Visit 1 or Visit 2 to allow for flexibility.
f After randomization, daily dosing in Part 2 from Visit 5 through Visit 8, inclusive. No onsite visit required after start of study medication at Visit 5 to start of allergen triad (Visit 6). Every effort should be made to conduct the study visits within the specified windows in Part 2. However, if necessary due to local COVID-19 safety requirements, visits may be performed outside of these windows in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance.
g Subjects should dose consistently at the same time of day, preferably in the morning and evening. Each dose of study drug should be taken while fasting (e.g., at least 1 h before breakfast/first meal of the day for the first dose, and at least 4 h after the previous meal for the second dose). Subjects should not consume food other than water for 1 h after dosing.
h Subjects will be asked to complete a daily diary to capture date and times of both meals and study drug administration.
i Pharmacokinetic sampling to be conducted predose on Visits 6, 7, and 8, and additionally at Visit 7 at approximately 1 (*+ 0.5 h)* h and 3 (*+/- 0.5 h) h* postdose. Subjects should be instructed to hold their daily dose of study drug on the morning of Visits 6, 7, and 8 and arrive at the clinic after an overnight fast. Exact times of dosing and PK sample collection will be documented.

4. Estimands

An estimand is the target of estimation to address the scientific question of interest posed by a study objective. The four 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.

Intercurrent Events

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

- For efficacy 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. This strategy aligns with the assumption that zavegepant is expected to confer benefits to the subject after study drug discontinuation. Thus, premature study drug discontinuation is ignored for these efficacy endpoints.

4.1. Primary Endpoint

Table 1: Primary Objective Estimand

Objective	**To evaluate the allergen-induced LAR 3 to 7 hours after the administration of the allergen inhalation challenge between subjects treated with zavegepant and placebo.**
Efficacy Endpoint	Maximum percentage decrease from baseline in FEV_1 at any time between 3 and 7 hours post-allergen challenge in the modified intent-to-treat (mITT) analysis set.
Summary	Difference in maximum percentage decrease from baseline in FEV_1 between the zavegepant and placebo groups using an ANCOVA model.
Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.

4.2. Secondary Endpoints

Table 2: Secondary Objective Estimands

1	**Objective**	**To evaluate the allergen-induced EAR 0 to 2 hours after the administration of the allergen inhalation challenge between subjects treated with zavegepant and placebo.**
	Efficacy Endpoint	Maximum percentage decrease from baseline in FEV_1 at any time between 0 and 2 hours post-allergen challenge in the mITT analysis set.

	Summary	Same as that of primary estimand, with respect to EAR.
	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.
2	Objective	To evaluate the AHR measured at 24 hours post-allergen challenge between subjects treated with zavegepant and placebo.
	Efficacy Endpoint	Shift from pre-allergen challenge (Visit 6) to post-allergen challenge (Visit 8) of PC_{20} in the mITT analysis set.
	Summary	Difference in shift from pre to post-allergen challenge between the zavegepant and placebo groups using an ANCOVA model.
	Intercurrent Events	Treatment policy strategy: All available assessments on the subject are used regardless of intercurrent events.
3	Objective	To assess the safety and tolerability of oral zavegepant.
	Endpoint	Various safety endpoints (i.e., adverse events, clinically significant laboratory abnormalities).
	Summary	Frequency by treatment group of safety endpoints for the safety analysis set.
	Intercurrent	Not applicable

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5. Analysis Sets, Treatment Groups, and Subgroups

5.1. Analysis Sets

Enrolled: The enrolled analysis set includes all subjects who sign the informed consent form (ICF) and are assigned a subject identification number by the IWRS.

Full: The full analysis set includes enrolled subjects who receive a randomization treatment assignment from the IWRS.

Safety: The safety analysis set includes subjects from the full analysis set who received at least 1 dose of study therapy. The safety analysis set will be used for all analyses of safety endpoints. Subjects will be analyzed according to the treatment actually received.

Modified Intent-to-Treat (mITT): The mITT analysis set includes safety subjects (received at least 1 dose of study therapy) that provided at least 1 non-missing post-baseline LAR assessment. Subjects will be analyzed according to randomized treatment assignment.

Follow-up: Safety subjects whose last contact date is in the follow-up analysis period. This analysis set is used to assess follow-up safety.

5.2. Treatment Groups

The two treatment groups are zavegepant and placebo. The safety analysis set is assessed by as-treated treatment group, the full and mITT analysis sets are assessed by as-randomized treatment group, and the enrolled analysis set is assessed overall.

If a subject receives ≥ 1 dose of planned randomized treatment then that subject is considered to have as-treated treatment group equal to as-randomized treatment group, and will be analyzed according to randomized treatment.

5.3. Subgroups

No subgroup analyses are planned.

6. General Aspects for Statistical Analysis

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

6.1. General Methods

Refer to the Core SAP for descriptive statistics, counting rules, rounding rules, dictionaries for coding AEs, medical history, and non-study medications.

- Unless otherwise specified, summaries will be presented for each treatment group and overall.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- Unless otherwise specified, listings will be sorted by randomization status (randomized, not randomized), which is not displayed, subject ID, and visit and/or assessment date (and time) if applicable.
- If multiple assessments are conducted at a given time point or visit, the non-missing value closest to the target date/time for the visit is used; in the case of a tie, the last value collected is used. All assessment results will be listed.

6.2. Key Definitions

- Baseline is the last non-missing observation prior to first administration of study drug unless otherwise specified.
- Change from baseline will be calculated as post-baseline value minus baseline value. If either the baseline or post-baseline value is missing, the change from baseline is set to “missing”.
- The Study Day is the day relative to the date of first administration of study drug, where Day -1 is the day before administration of zavegepant and Day 1 is the day of first administration of study drug.
- Study day will be calculated as:
    - Study day = date of assessment – date of first administration of study drug +1 if the date of assessment is on or after the date of first study drug administration; Otherwise: Study day = date of assessment – date of first administration of study drug.
- Follow-up day will be calculated from the study drug last date as:
    - Measurement date – study drug last date, if measurement date ≥ study drug last date + 1; otherwise: Measurement date – study drug last date – 1, if measurement date < study drug last date + 1.

6.3. Missing Data

All analyses will be based on observed data unless otherwise specified. For the purposes of assessing treatment emergence for AEs or classifying medications into prior/concomitant, the algorithms described in Section 7.1.2.3 of the Core SAP will be used to impute partially and completely missing dates.

6.4. Visit Windows

All subjects are to adhere to the protocol-specified visit schedule in Table 2. Visits will be analyzed as captured in the database, no visit windows will be assigned.

7. Disposition, Demographic, Other Baseline Characteristics and Medication

7.1. Analysis Sets

The number of subject in each analysis set described in Section 5.1 is tabulated.

A by-subject listing of analysis sets is provided for the enrolled analysis set, and an administrative listing of randomization scheme and codes is provided for all randomization numbers and block numbers, even those not assigned to a subject. Refer to the Core SAP for listing contents.

7.2. Enrollment

Enrollment by country and site is tabulated for the enrolled analysis set. Refer to the Core SAP for more details.

7.3. Subject Disposition and Withdrawals

Subject disposition is based on the “Eligibility Criteria,” “Informed Consent,” and “Subject Disposition” CRFs, unless otherwise noted.

A by-subject listing of subject disposition will be provided for the enrolled analysis set based on the “Subject Disposition” and “Informed Consent” CRFs and includes the following: date informed consent was signed, protocol version, study completion status (yes, no, ongoing); reason for not completing the study, including specify text for “other” and AE preferred terms (PTs); study drug start date; and last contact date.This listing also identifies subjects who terminated the study prematurely due to COVID-19.

7.3.1. *Subject Disposition from Enrollment to Randomization*

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

- Randomized
- Not randomized
    - Reasons for discontinuation (i.e., not completing the study), including not reported. For subjects whose reason is screen failure due to inclusion/exclusion criteria, the reasons for screen failure are also included from the "Eligibility Criteria” CRF
- Not randomized and terminated the study prematurely due to COVID-19. This has the same subcategories as “Not randomized.”

7.3.2. *Subject Disposition from Randomization to Treatment*

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

- Treated with study drug (identified as those with non-missing study drug start date)
- Not treated with study drug (identified as those with missing study drug start date)
    - Reasons for discontinuation (i.e., not completing the study), including not reported
- Not treated with study drug and terminated the study prematurely due to COVID-19. This has the same subcategories as “Not treated with study drug.”

7.3.3. *Subject Disposition from Treatment to End of Study/Follow-up*

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

- Completed the study (identified as those with “yes” response to the question “Did the subject complete the study?”)
- Did not complete the study (identified as those with “no” response to the question “Did the subject complete the study?”)
    - Reasons for not completing the study, including not reported
- Terminated the study prematurely due to COVID-19. This has the same subcategories as “Did not complete the study.”

7.4. Protocol Deviations

A relevant protocol deviation is a deviation from the protocol which is programmed from the database and which could potentially affect the interpretability of the study results. This type of deviation includes but is not limited to:

- Eligibility
- Subject management

The frequency table of relevant protocol deviations displays the number and percentage of subjects in deviation categories and subcategories by deviation type (e.g., eligibility, subject management) for the full analysis set. Results are displayed for all deviations, even those with 0 counts, unless otherwise specified. See Section 6.2.4.1 of the Core SAP for further details.

A by-subject listing of relevant, programmable protocol deviations is provided for the enrolled analysis set. Relevant protocol deviations are outlined in Section 16 .

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

A Microsoft Excel file of protocol deviations is provided by the data management vendor from the clinical trial management system (CTMS). This file serves as the raw data source of protocol deviations, and classifies deviation severity as major, minor, or exclude. Significant protocol deviations are defined as those with major severity. A footnote describes the raw data source and how significant protocol deviations are identified, e.g., “Significant protocol deviations are those with major severity reported by the data management vendor in the clinical trial management system.”

7.5. Demographic and Baseline Characteristics

A summary of demographic and baseline characteristics will be presented by treatment group and overall using the safety analysis set. Descriptive statistics will be calculated for continuous variables (age, BMI, height, and weight) at baseline. Frequency counts and percentages will be tabulated for categorical variables (age category, gender, childbearing potential if female, ethnicity, race, country, BMI category).

Demographic and baseline characteristics will also be listed by subject for the enrolled analysis set. Weight, height, and BMI will be listed with vital signs as detailed in Section 10.3.

7.6. Alcohol Consumption and Smoking History

Alcohol consumption and smoking history will be listed by subject for the enrolled analysis set.

7.7. Medical History and Concomitant Diseases

Medical history as recorded at baseline will be summarized by treatment group and overall for the safety analysis set using the number and percentages of subjects reporting each system organ class (SOC) and preferred term (PT). Medical history will be sorted by descending overall total by SOC and PT within each SOC using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 24 or later in the summary table.

Medical history will be listed by subject for the enrolled analysis set.

7.8. Non-Study Medications

Non-study medications taken during the course of the study will be presented in tabular form for the safety analysis set using Anatomical Therapeutic Chemical (ATC) classification level 4 terms (ATC4) and preferred name via the World Health Organization (WHO) Drug Global B3 March 2021 or later for the following types:

- Prior medications (previous, current)
- Concomitant medications

The definitions of medication types are in Section 6.2.6.3 of the Core SAP. Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. Imputed medication start and stop dates are used to assign non-study medication type (previous, current, concomitant, follow-up) to all non-study medications. Refer to the Core SAP for non-study medication start and stop date imputation. Subjects will be counted only once for each ATC4 term in the event that they have multiple records of the same ATC level in the database.

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

7.8.1. *Prior Medications*

Prior medications will be summarized descriptively by treatment group and overall for the safety analysis set in two tables: one for prior medications (including both previous and current) and one for current medications.

7.8.2. *Concomitant Medications*

Concomitant medications will be summarized descriptively by treatment group and overall for the safety analysis set.

7.9. Extent of Exposure

Study drug is zavegepant 300 mg daily, i.e., six 25 mg softgel capsules twice daily, taken in the morning and the evening. Study drug is dispensed in a wallet-type blister pack with a unique wallet ID and 8 wallets are placed into a subject specific kit with a unique kit ID. Each wallet covers 4 days of morning dosing (6 capsules) and evening dosing (6 capsules) dosing, for a total of 48 capsules. Sites will record the kit and wallet IDs dispensed to each subject on the Drug Accountability CRF.

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

Study drug exposure is tabulated as continuous or categorical variables by treatment group and overall for the safety analysis set and includes the following parameters:

- Time from study drug start to last contact (days), derived as: last contact date – study drug start date + 1
- Time on study drug (days), derived as: study drug end date – study drug start date + 1
- Time on study drug categories (weeks): 1, 2, 3, 4, or > 4
- Cumulative study drug exposure (mg), derived by summing {number of capsules × 25} across records with complete study medication start dates
- Average study drug exposure (mg per day), derived as cumulative study drug exposure/time on study drug (days)
- Total study drug exposure (mg) summed across all subjects, derived by summing cumulative exposure across all subjects
- Total study drug exposure (patient-years), derived by summing (study drug end date – study drug start date + 1)/365.25 across all subjects.

Study drug accountability is tabulated by treatment group and overall for the safety analysis set that includes the number and percentage of subjects in the following category:

- Study drug taken but subject not randomized
- Kit dispensed and all 8 wallets returned
- Kit dispensed and all 8 wallets not returned
    - Reason for wallets not being returned
- Number of capsules returned
- Number and percentage of subjects who took > 12 capsules on any 1 day
- Any partial/missed doses
- Compliance < 80%, derived as: (number of capsules dispensed – number of capsules returned)/(number of capsules expected to be taken) x 100%
- No study drug taken for ≥ 3 days (not necessarily consecutive) in any 1 week
- Incorrect study drug taken: all the time, or at least once

Incorrect study drug at least once means subject is (1) randomized to placebo group but received >=1 dose of study drug from study drug kit/container or (2) randomized to study drug group but received >=1 dose of study drug from placebo kit/container.

Incorrect study drug all the time means subject received incorrect study drug at least once (as defined above) and never received any randomized study drug.

A by-subject listing of study drug accountability is provided for the safety analysis set. Additionally, a by-subject listing of study drug accountability for partial/missed doses is provided for the safety analysis set.

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

8. Efficacy

Efficacy will be measured via spirometry and lung function assessments. These assessments will be performed after each study dose treatment at Visit 5, Visit 6, Visit 7, and Visit 8. Methacholine PC_{20} and airway inflammation will be assessed before and after study dose treatment, and allergen-induced methacholine PC_{20}, allergen-induced bronchoconstriction, and allergen-induced airway inflammation will be assessed following allergen challenges. All efficacy assessments will be performed on the mITT analysis set.

The methacholine inhalation test will be performed at Visit 2, Visit 4, Visit 5, Visit 6, and Visit 8. This test will measure FEV_1 at 30 and 90 seconds after each inhalation and, if necessary, at 180 and 300 seconds and beyond until the lowest response is captured. The test is terminated when a fall in FEV_1 of at least 20% (lowest post diluent FEV_1 versus lowest post methacholine concentration FEV_1) occurs, and the methacholine PC_{20} is calculated. The PC_{20} assessment will be performed at the start of each treatment period, then 24 hours before and 24 hours following allergen challenge as a measure of AHR.

The allergen inhalation challenge will be performed at Visit 3 and Visit 7. At Visit 3, doubling concentrations of allergen will be given until a 20% decline in FEV_1 is measured 10 minutes post-allergen inhalation versus baseline FEV_1. The FEV_1 will then be measured at regular intervals: 10, 20, 30, 45, 60, 90, 120 minutes, and 3, 4, 5, 6, and 7 hours after allergen inhalation to confirm both ≥20% fall in FEV_1 (EAR) and ≥15% fall in FEV_1 (LAR). The same final 3 doses of allergen administered during the screening period are administered during the dosing period challenge. The EAR is taken to be the largest fall in FEV_1 wihin 2 hours after allergen inhalation and the LAR is taken to be the largest fall in FEV_1 between 3 and 7 hours after allergen inhalation. The concentration of allergen that resulted in a 20% decline in FEV_1 will be selected for the allergen challenges at Visit 7 and Visit 8.

Sputum induction will be performed at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8. It will be performed 24 hours before allergen challenges and at 7 and 24 hours after allergen challenges, at the start of each treatment period, again at 24 hours before allergen challenges, and at 7 and 24 hours after allergen challenges. CCI [redacted]

Allergy skin testing will be performed at Visit 1 or Visit 2. It will determine the allergen that is given to each patient in the inhalation allergen challenge. If an allergen provokes an allergic reaction, a raised itchy bump (wheal) and redness (flare) develops. The size of the wheal will be measured and recorded with a ruler in millimeters in the horizontal and vertical directions, perpendicular to each other after approximately 15 minutes. The size of the wheal for each antigen will be recorded. A reaction greater than 2 x 2 mm will be regarded as positive, provided that the positive and negative controls are appropriately positive (histamine) and negative (diluent), respectively.

Allergy skin titration testing will be performed at Visit 1 and Visit 2. It will identify the lowest titration of allergen that causes a skin wheal at least 2 x 2 mm in size. The diameter of each wheal is measured in 2 perpendicular directions after 10 minutes. The average wheal diameter for each dilution in the horizontal and vertical directions is recorded. The weakest dilution of allergen that produces an average wheal of at least 2 x 2 mm is the “skin test endpoint.” This measurement is used to calculate the starting allergen dose for inhalation.

8.1. Primary Efficacy Endpoint and Analysis

8.1.1. *Late Asthmatic Response*

The primary efficacy endpoint is allergen-induced LAR, as assessed by maximum percentage decrease in FEV_1 between 3 and 7 hours post-allergen challenge at Visit 7, compared between zavegepant and placebo using analysis of covariance (ANCOVA). The maximum percentage decrease is the difference between the baseline (pre-allergen challenge) FEV_1 at Visit 7 and lowest FEV_1 between hours 3 and 7 at Visit 7 divided by the baseline value from Visit 7. An ANCOVA model based on the decrease in FEV_1 between 3 and 7 hours post-allergen challenge with treatment as a factor and baseline LAR as a covariate will be fitted. The point estimate and 95% CIs will be reported for the difference in LARs comparing zavegepant and placebo.

The LAR will also be assessed by an area under the curve (AUC) for the percent decrease in FEV_1 value between 3 to 7 hours. The AUC for percent decrease in FEV_1 will be compared between zavegepant and placebo using ANCOVA. ANCOVA model based on the AUC for the percent decrease in FEV_1 between 3 and 7 hours at Visit 7 with treatment as a factor and baseline (pre-allergen challenge) FEV_1 at Visit 7 as a covariate to adjust for AUC will be fitted. AUC will be calculated using the trapezoidal method to estimate the areas over the observation time. The point estimate and 95% CIs will be reported for the difference in AUCs comparing zavegepant and placebo.

Additional supportive endpoints, including minimum absolute FEV_1 value in 3 to 7 hours and AUC of the absolute FEV_1 values in 3 to 7 hours at Visit 7 will also be analyzed. The minimum absolute FEV_1 will be the lowest value between hours 3 and 7 post-allergen challenge at Visit 7 and AUC will be calculated as described above. Both endpoints will be compared between zavegepant and placebo using an ANCOVA model with treatment as a factor and baseline FEV_1 at Visit 7 as a covariate. The baseline value is the measurement prior to dosing at Visit 7. The point estimate and 95% CIs will be reported for the difference in minimum absolute FEV_1 or AUC when comparing zavegepant and placebo.

The time-response curve of allergen-induced percentage decrease in FEV_1 may be plotted for baseline (screening allergen challenge) and Visit 7.

8.2. Secondary Efficacy Endpoints and Analyses

The secondary efficacy endpoints are the allergen-induced EAR assessed as maximum percentage decrease in FEV_1 between 0 and 2 hours after the administration of allergen inhalation challenge and allergen-induced change in AHR (methacholine PC_{20}) at 24 hours post-allergen challenge.

8.2.1. *Early Asthmatic Response*

The maximum percentage decrease in FEV_1 between 0 and 2 hours at Visit 7 will be compared between zavegepant and placebo using ANCOVA. The maximum percentage decrease is the difference between the baseline (pre-allergen challenge) FEV_1 at Visit 7 and the lowest FEV_1 between 0 and 2 hours at Visit 7 divided by the baseline value from Visit 7. An ANCOVA model based on the decrease in FEV_1 between 0 and 2 hours at Visit 7 with treatment as a factor and baseline FEV_1 at Visit 7 as a covariate will be fitted. The baseline value is the measurement prior to dosing at Visit 7. The point estimate and 95% CIs will be reported for the difference in AUCs comparing zavegepant and placebo.

Additionally, as a supportive analysis for the EAR, the AUC for percent decrease in FEV_1 between 0 and 2 hours at Visit 7 will be compared between zavegepant and placebo using ANCOVA. AUC will

be calculated as described in Section 8.1.1. An ANCOVA model based on the AUC for the percent decrease in FEV_1 between 0 and 2 hours at Visit 7 with treatment as a factor and baseline (pre-allergen challenge) FEV_1 at visit 7 as a covariate will be fitted. The baseline value is the pre-allergen challenge measurement at Visit 7. The point estimate and 95% CIs will be reported for the difference in AUCs comparing zavegepant and placebo.

The minimum absolute FEV_1 value in 0 to 2 hours and AUC of the absolute FEV_1 values in 0 to 2 hours at Visit 7 will also be analyzed. AUC will be calculated as described in Section 8.1.1. The minimum absolute FEV_1 will be the lowest value between hours 0 and 2 post-allergen challenge at Visit 7. Both endpoints will be compared between zavegepant and placebo using an ANCOVA model with treatment as a factor and baseline FEV_1 at Visit 7 as a covariate. The baseline value is the measurement prior to dosing at Visit 7. The point estimate and 95% CIs will be reported for the difference in minimum absolute FEV_1 or AUC comparing zavegepant and placebo.

8.2.2. *Methacholine PC_{20}*

The methacholine PC_{20} will first be normalized by log transformation. The shift will be measured as the difference in the concentration of methacholine required to cause a 20% decline in FEV_1 pre- and post-allergen exposure. Specifically, shift in PC_{20} is calculated as post-allergen challenge – pre-allergen challenge (Visit 8 – Visit 6), and baseline shift in PC_{20} will be calculated as post – pre (Visit 4 – Visit 2). The pre- versus post-allergen shift in PC_{20} will be compared between zavegepant and placebo using ANCOVA. The ANCOVA model will include treatment as a factor and baseline shift as a covariate. Pre- and post-allergen challenge methacholine PC_{20} will be summarized descriptively with geometric mean and range.

The methacholine PC_{20} geometric means may be presented graphically.

CCI [redacted]

9. Pharmacokinetics

Not applicable. The PK data will not be analyzed for this CSR.

10. Safety

All safety analyses will be performed using the safety analysis set. Safety will be assessed based on AEs, clinical laboratory data, spirometry, S-STS, physical examinations, vital signs.

Analysis periods are pre-treatment, on-treatment, and follow-up. Refer to Core SAP about slotting safety parameters into analysis periods.

Safety parameters are tabulated descriptively as continuous variables at baseline and each scheduled visit over time during the pre-treatment, on-treatment, and follow-up analysis periods.

By-subject listings of safety parameters are described in subsections.

10.1. Adverse Events

All reported AEs will be coded using the MedDRA coding dictionary version 24.0 or later, andsummarized by System Organ Class (SOC) and Preferred Term (PT),.

Refer to the Core SAP for AE start date imputation, AE counting rules, definition of AEs related to study drug, definition of AEs of special interest, and TLF contents.

Tables present number and percentage of subjects experiencing AEs by SOC and PT, unless specified otherwise. AEs are tabulated in descending order of overall frequency within SOC and PT.

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

10.1.1. *Deaths*

Deaths are identified from the following sources:

- AE CRF: PT or reported term containing “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?”); or non-missing death date.
- Subject Disposition CRF: study non-completion reason of death.

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

10.1.2. *AE Overview*

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

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

10.1.3. *On-treatment AEs*

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

- AEs by intensity (total, mild, moderate, severe, moderate or severe, not reported)
- AEs related tostudy drug by intensity

- AEs by relationship to study drug (related, possibly related, unlikely related, not related, not reported)
- SAEs
- AEs leading to study drug discontinuation

10.1.4. *Follow-up AEs*

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

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

10.2. Laboratory Evaluations

Laboratory parameters include, but are not limited to, assessments in Table 3.

Table 3. Laboratory Parameters

Hematology	**Serum Chemistry**	**Urinalysis**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	albumin ALT ALP AST BUN or urea carbon dioxide creatinine eGFR creatine phosphokinase electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT glucose LDH total bilirubin direct and indirect bilirubin total cholesterol LDL HDL triglycerides	appearance pH protein glucose ketone bodies specific gravity urobilinogen bilirubin occult blood nitrates leukocytes
Pregnancy test: A human chorionic gonadotropin (hCG) blood test will be conducted on all WOCBP at screening; an hCG urine test will be conducted at all subsequent visits according to **Error! Reference source not found.**.		
Urine drug screen: Drugs of abuse include, but are not limited to, amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, and PCP (see **Error! Reference source not found.** Assessments). Retesting for positive results that are exclusionary is not allowed**.**		
Sputum test: Refer to Section **Error! Reference source not found.** of protocol.		

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; GGT=gamma-glutamyl transpeptidase; Hb=hemoglobin; HBV=hepatitis B; Hct= hematocrit; HDL=high-density

lipoproteins; LDH=lactate dehydrogenase; LDL=low-density lipoproteins; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PCP=phencyclidine; pH=potential hydrogen; RBC=red blood cell; WBC=white blood cell; WOCBP=women of childbearing potential.

Blood and urine samples will be analyzed at a central laboratory facility. Each subject will be assessed with the following laboratory tests and parameters:

- Clinical laboratory samples will be collected Visit 1, Visit 5, Visit 8, and at Follow-Up.
- Urinalysis samples will be collected at Visit 1, Visit 5, and Visit 8.
- A serum pregnancy test will be conducted at Screening and urine pregnancy testing at Visit 5 and Visit 8.
- Urine drug testing will be performed at Visit 1 only.

Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated.

TLFs show data in the Systeme Internationale (SI) unit system, if applicable. Tables present results by treatment group and overall, and laboratory tests alphabetically within laboratory test group, as applicable.

Clinically significant laboratory test abnormalities will be identified as Grade 3 to Grade 4 laboratory test results graded accordingly to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (2017), if available. Otherwise, if CTCAE grades are not available, then results will be graded according to numeric laboratory test criteria in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs. If a subject has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported in the lab abnormality summary table. Refer to the Core SAP for laboratory tests of clinical interest for analyses, including identification of those with toxicity grades.

10.2.1. *Laboratory Test Abnormalities*

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

- Worst (highest) on-treatment laboratory test abnormality for each graded laboratory test.
- Laboratory test toxicity grade shift from baseline to the worst on-treatment toxicity grade for each graded laboratory test.

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

10.2.2. *Liver Function Test Elevations*

Refer to the Zavegepant Core SAP for LFT elevation categories and additional details.

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

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

LFT ULN Shifts from Baseline to Worst Elevation

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

LFT Plots

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

10.2.3. *Laboratory Test Changes from Baseline*

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

10.2.4. Laboratory Test Listings

All laboratory test listings will be based on the enrolled analysis set.

A by-subject listing of the following select laboratory tests is provided for subjects with at least one laboratory assessment of grade 3 or 4 abnormality or a positive pregnancy test result: hematology results, serum chemistry results, and urinalysis results. If there is a positive pregnancy test, defined as a serum or urine pregnancy test with either (1) “positive” character value, or (2) numeric value $\geq$ 25 U/L. the listing will also include all pregnancy test results over time.

Refer to Section 6.4.2.6 of the Core SAP for listing contents as applicable to this study.

A by-subject 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 Section 6.4.2.6 of the Core SAP for listing contents as applicable to this study.

10.3. Vital Signs and Physical Measurements

Vital signs will be taken at Visit 1, Visit 5, Visit 6, Visit 7, and Visit 8.

The vital signs to be captured are systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature. Temperature will be presented in summaries and listings in Celsius (Temperature (in °C) = 5/9 (Temperature [in °F]-32)).

10.3.1. *Vital Sign and Physical Measurement Change from Baseline*

Values and changes from baseline in vital signs and physical measurements will be tabulated descriptively as continuous variables at baseline and each scheduled visit in the on-treatment analysis period.

10.3.2. *Vital Sign and Physical Measurement Abnormalities*

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

10.4. Spirometry

Spirometry will be measured at every visit during Part 1 (Screening) and after each study dose treatment at Visits 5 through 8. Spirometry is used to monitor baseline lung function and gauge the level of bronchoconstriction during methacholine and allergen challenges. Measurements include: forced vital capacity (FVC) in liters, FEV1 in liters, and the percentage of predicted FEV1 value. Results are tabulated

pre-treatment and on-treatment for the safety analysis set. On-treatment data will also include changes from baseline.

10.5. S-STS

The S-STS is a prospective, clinician-administered rating questionnaire with 16 patient-reported questions and 6 clinician-reported questions that tracks both treatment-emergent suicidal ideation and behaviors. The S-STS will be performed at Visit 1, Visit 5, and Visit 8.

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

Values and changes from baseline in the self-reported S-STS ideation subscale, behavior subscale, and total score are tabulated descriptively as continuous variables at baseline and the worst (highest) score in the analysis periods. The table also presents the number and percentage of subjects in the worst (highest) score change from baseline category (i.e., < -1, -1, no change, 1, >1) in analysis periods for the ideation subscale, behavior subscale, and total score.

Results are tabulated on-treatment for the safety analysis set.

10.6. Safety Narratives

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

- Deaths for the enrolled analysis set
- On-treatment and follow-up SAEs for the safety analysis set, regardless of relationship to study drug
- AEs leading to discontinuation of study drug across all analysis periods for the safety analysis set, regardless of relationship to study drug
- On-treatment events of special interest for the 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 AEs, i.e., PTs containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
    - Cardiovascular AEs
    - Suicidality AEs

Refer to the Core SAP for additional details. The listing flags subjects with select events.

Should the criteria stated in the Biohaven Zavegepant Safety Narrative Scope conflict with the criteria above, the Biohaven Zavegepant Safety Narrative Scope will take precedence.

10.7. COVID-19 Impact

COVID-19 impact will not be analyzed for the CSR.

11. Conventions

11.1. Derived Dates

Derived dates for defining analysis periods are defined as follows:

- Study drug start date: Date of first dose of study drug from Study Drug Accountability CRF.
- Imputed study medication stop date: If the study medication stop date is (1) non-complete or (2) complete but before the study medication start date, then the imputed stop date is set to the study medication start date. Otherwise, the imputed stop date is set to the complete study medication stop date. Derived only for subject dosing diary 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 and (2) imputed study medication stop dates. Both (1) and (2) are from subject dosing diary records with number of capsules taken > 0.
- Study drug last date: Study drug end date derived only for subjects with non-missing response to the question “Did the subject complete the study (including the follow-up visit)?” on the Subject Disposition CRF. Thus, in an interim analysis, all post-baseline data are included for a subject who is still on study. At the last database lock, the study drug last date is equal to the study drug end date.
- COVID-19 visit date: (1) Complete visit date, if it exists; (2) otherwise, complete date the visit was planned to occur for a missed visit.
- 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 stop; COVID-19 visit for in-person or remote visits; ECG; informed consent; laboratory test collection; non-study medication start or stop; physical exam; physical measurement; procedure; questionnaire; study medication start or stop; vital sign; visit. If the last contact date is after the most recent raw database creation date, then it is set to the most recent raw database creation date.
- Death date: Last contact date derived only for subjects who died (see Section 11.1).

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

11.2. Analysis Periods

Analysis periods are defined as follows:

- Pre-treatment: measurement date/time on or before the study drug start date. This period is used to derive baseline values and to assess safety endpoints. Note that all measurements are pre-treatment for subjects in the enrolled analysis set with missing study drug start date. Note that AEs with imputed start date equal to the study drug start date are NOT part of this period.
    - Pre-treatment will include Visits 1 – 5 / Study Days -29 – 1
- On-treatment: measurement date/time after the study drug start date through the study drug last date + 7 days or ending at the follow-up visit, whichever is earliest. This period is used to assess safety endpoints on treatment. Note that AEs with imputed start date equal to the study drug start date are part of this period.

  - On-treatment will include Visits 6 – 8 / Study Days 1 – 28

- Follow-up: measurement date after the study drug last date + 7 days or starting at the follow-up visit, whichever is earliest. This period is used to assess safety endpoints during follow-up.

  - Follow-up will include Visit 9 / Study Days 35 – 41

See Section 11.1 for derived dates for determining analysis periods. If measurement time is missing, not collected, or not applicable for a parameter, then the measurement date is compared to the derived date.

12. Interim Analyses

No interim analyses are planned for this study.

13. Changes from Analysis Planned in Protocol

The Treated Population is defined in the study protocol. However, it has been renamed the Safety Population in the SAP.

One additional study populations were added that are not defined in the study protocol, the Follow-up population.

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907) .

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. Shells

The TFL shells will be provided as a separate document.

16. Appendices

Appendix A Relevant Protocol Deviations

Relevant eligibility protocol deviations include the following categories:

- Respiratory disease other than mild intermittent asthma
- Baseline FEV_1 < 70% of predicted value
- Score on the Sheehan-Suicidality Tracking Scale (S-STS) at screening > 0
- Methacholine challenge (PC20 > 16 mg/mL)
- History of liver disease or viral hepatitis
- History of HIV
- Use of tobacco products and/or vaping products within the previous 12 months or smoking history > 10 pack years.
- Positive drug screen
- Findings out of range, defined any as any of the following subcategories:
  - At any time during the study:
    - Females with a positive pregnancy test
  - <u>During pre-treatment period:</u>
    - ALT ≥ 1.5x ULN
    - AST ≥ 1.5x ULN
    - Direct bilirubin ≥ 1.5x ULN
    - Indirect bilirubin ≥ 1.5x ULN
    - Total bilirubin ≥ 1.5x ULN
    - BMI ≥ 33 kg/m^2
    - Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 $mL/min/1.73m^2$
    - Systolic blood pressure > 150 mmHg
    - Diastolic blood pressure > 100 mmHg

Relevant subject management protocol deviations include the following categories:

- Study drug dosing
  - < 80% compliance
- Study drug dosing error, defined as any of the following subcategories:
  - Study drug taken but not randomized
  - Study drug actually received different from randomized treatment assignment
- Missed study exit visit
- Missed methacholine challenge, skin allergen challenge, allergen challenge
- Washout period after methacholine challenge and sputum induction on Visit 4 other than 2-4 weeks
- Visit 5 methacholine challenge FEV1 < 90% of baseline for FEV1
- <u>Visit 9 (follow up onsite visit) conducted outside 7-10 day after last study treatment window</u>
- Use of any prohibited medications (refer to Table 9.1 in the protocol) on or after informed consent
  - CGRP targeting medications
  - Anti-IgE therapy
  - Allergy immunotherapy
  - Investigational drug
  - Systemic, inhaled, topical nasal steroids
  - Immunosuppressives
  - Anticoagulants
  - Theophylline
  - Nedocromil or cromoglycate
  - Modafinil

- St. John's wort
- Atypical antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone
- Mood stabilizers such as lithium, lamotrigine or divalproex/valproic acid/valproate
- Strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers such as clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole, apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort
- Potent P-glycoprotein (P-gp) inhibitors or inducers such as amiodarone, clarithromycin, cyclosporine, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ritonavir, verapamil
- Leukotriene modifiers
- Long-acting beta agonists
- Long-actine anticholinergics
- Antimuscarinics
- Non-steroidal anti-inflammatory drugs