Biohaven Pharmaceuticals

Protocol BHV3500-203

BHV3500-203: Phase 2/3: Double-Blind Randomized, Placebo Controlled, Safety and Efficacy Trial of Zavegepant (BHV-3500) Intranasal (IN) for Hospitalized Patients with COVID-19 Requiring Supplemental Oxygen

Statistical Analysis Plan

Version 4.0

Date: 17-Oct-2022

SIGNATURE PAGE

Protocol Title:	BHV3500-203: Phase 2/3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of Zavegepant (BHV-3500) Intranasal (IN) for Hospitalized Patients with COVID-19 Requiring Supplemental Oxygen
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Sponsor Approval

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

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

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

Sponsor Signatories:

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REVISION HISTORY

Version	Description of Change
1.0	Original issue (27-Aug-2020) based on Protocol Version 4.0
2.0	Amended version (21-Jan-2021) based on Protocol Version 6.0 General: Applied chemical notation throughout. Section 2.1: Updated Figure 1 based on the latest protocol version. Section 2.4: Specified that SAP Version 2.0 is based on Protocol Version 6.0, which replaced the Hochberg procedure with the Holm procedure for testing the key secondary endpoints. Section 3.2.2.1: Modified the efficacy endpoint for Objective 2 in Table 2 to be consistent with the protocol. Modified the efficacy endpoint and summary for Objective 13 to clarify the analysis subset. Section 4.1: Modified text to be consistent with the protocol. Section 5.2: Changed "Hochberg" to "Holm". Section 6.2.1: Specified that the administrative listing of randomization scheme and codes also displays block number. Section 6.2.2: Specified that age group is based on age at informed consent. Section 6.2.5: Added summaries for the PK analysis set. Modified the definition of baseline. Sections 6.2.5.1 and 6.4.3: Changed pulse rate to heart rate. Section 6.3: Changed "Not applicable" to "ANOVA" for endpoint S19 in Table 6. Section 6.3.1.1: Changed "age group" to "randomized age group" as fixed effect in 2-way ANCOVA and ANOVA. Section 6.3.2.1: Added 2 additional subcategories of missing data to the table of 6POSRS rating as a descriptive categorical variable over time. Section 6.3.3: Changed "Hochberg" to "Holm" and modified the algorithm accordingly. Section 6.3.3.4: Changed "Hochberg" to "Holm". CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] Section 6.4.1.1: Defined death day and added it to the deaths listing. Section 6.4.2: Removed the eGFR MDRD formula. Specified that eGFR data from the eCRF are not used in analyses described in proceeding subsections. Sections 7.3.1 and 7.3.2: Specified that values derived in step 2 are independent of steps 3 and 4.
3.0	Amended version (03-Jun-2022) based on Protocol Version 7.0 General: Changed "Zavegepant Core SAP" to "Core SAP". Modified language to use phrases like "table of <specified endpoint> is provided" instead of "<specified endpoint> is tabulated". Changed "follow-up analysis set" to "follow-up safety analysis set". Changed "stop date" to "end date". Section 1: Specified that this SAP references the Rimegepant/Zavegepant Core SAP. Section 1.2: Specified that if the study is terminated prematurely due to low enrollment, then only the last planned analysis will be conducted unblinded. Section 2.4: Specified that SAP Version 3.0 is based on Protocol Version 7.0.

	Section 3.1.2.2: Removed objectives #1-17 as per Protocol Version 7.0. Section 3.1.2.3: Added objectives #1-17 from Section 3.1.2.2, and modified the language for exploratory objective #10 as per Protocol Version 7.0. Sections 3.2: Specified additional details for data sources for endpoints. Sections 3.2.2.2 and 3.2.3: Removed objectives #1-17 in Table 3. CCI [redacted] Section 4.1: Changed "follow-up analysis set" to "follow-up safety analysis set". Added the full analysis set. Section 4.2: Specified the full analysis set. Section 6.1.1.1: Modified treatment group presentation in tables. Section 6.2: Referenced the Core SAP for TLF contents. Section 6.2.1: Changed the frequency table of inclusion and exclusion from the efficacy analysis set and by-subject listing of subjects excluded from the efficacy analysis to be based on the full analysis set instead of the randomized analysis set. Section 6.2.2: Changed the frequency table of enrollment by country and site to use the full analysis set instead of the randomized analysis set. Section 6.2.3: Added a footnote to subject disposition listings about the last contact date. Section 6.2.4: Specified that results are based on the Protocol Deviations and Violations eCRF. Changed the frequency table to be based on the full analysis set instead of the randomized analysis set. Defined significant protocol deviations. Specified listing contents. Section 6.2.5: Removed baseline characteristics tables for the PK analysis set. Removed baseline derivations and instead referenced the Core SAP. Changed "randomized analysis set" to "full analysis set" for baseline characteristics tables. Added a frequency table of randomized age group for the randomized analysis set. Section 6.2.5.4: Removed the frequency table of non-study prior medications. Section 6.2.6.1: Removed compliance-related parameters from the exposure table. Section 6.2.6.2: New section "Treatment Compliance". Added a table and by-subject listing of treatment compliance for the safety analysis set based on compliance-related parameters formerly in the exposure table. Section 6.2.6.3: Renumbered from former 6.2.6.2. Specified the display of medications according to analysis set. Section 6.3.1: Section title ("Efficacy Overview") added for organizational purposes. Modified Table 6 title and contents to align with changes in Sections 3.1 and 3.2, including adding exploratory endpoints E18 and E19. Section 6.3.1.2: Specified that statistics from the CMH test are displayed in the same table as the descriptive statistics. CCI [redacted]

	CCI [redacted] Section 6.4: Specified treatment group presentation for analysis sets, and sort order of AEs. Changed references to other secondary endpoints throughout. Section 6.4.1: Added references to the Core SAP for AE end date imputation, definitions of TEAEs, AEs related to study drug, and AEs of special interest, and TLF contents. Specified the sort order of AEs in tables by SOC and PT. Section 6.4.1.1: Modified the death algorithm. Specified that deaths are slotted into analysis periods according to the death date/time. Section 6.4.6: Specified the display of MedDRA PTs corresponding to "other" procedures. Specified that procedures are slotted into analysis periods according to both imputed procedure start and imputed procedure end dates. Removed references to procedure type. Sections 6.4.6.1 and 6.4.6.2: Removed. Section 6.4.6.2: Renamed procedure types of prior and concomitant to pretreatment and on-treatment, respectively. Modified algorithms to handle missing study drug last date. Section 6.4.9: Specified that at each analysis visit, the denominator is based on the number of evaluable subjects, and provided its definition. Section 6.4.10: Added a by-subject listing of safety narrative subject identifiers. Section 7.1: Modified the derivation of the study drug last date/time. Added the initial hospitalization return date, imputed procedure start date, and imputed procedure end date. Section 7.2: Removed the definitions of pretreatment, on-treatment safety, and follow-up safety analysis periods, and instead referenced the Core SAP. Section 7.3: Renumbered Table 7 as Table 8. Section 9.2: New section "Procedures in Analysis Periods". Section 9.3: Renumbered from previous Section 9.2. Modified the definition of intensive care day to use imputed AE end date per Core SAP.
4.0	Amended version (17-Oct-2022) based on Protocol Version 7.0 Signature page: Modified PPD title. Replaced PPD with PPD and PPD with PPD. Added "abbreviated" in front of CSR. Abbreviations: Removed ANCOVA, ANOVA, AR(1), ASE, AUC, BLQ, Cmax, CMH, CV, DBP, eDISH, MCAR, MMRM, MNAR, NC=M, and SE. Section 1: Specified that the study was terminated prematurely in 4Q2022 due to low enrollment, an abbreviated CSR will be provided instead of a CSR, and the SAP is being amended from Version 3.0 to 4.0 to reduce the number of TLFs needed for the abbreviated CSR. Section 2.4: Specified that SAP 4.0 is based on BHV3500-203 Protocol Version 7.0. Section 3.2: Specified that study drug discontinuation is handled with a "treatment policy strategy" for efficacy objectives. CCI [redacted] Specified that the "treatment policy" strategy for safety objectives is applied to select endpoints. CCI [redacted] Section 3.2.1: Removed treatment group comparisons and references to randomized age group from Table 1. Section 3.2.2.1: Removed treatment group comparisons and references to randomized age group from Table 2

	Section 3.2.2.2: Removed references to randomized age group from Table 3. Removed references to the on-study safety analysis period in Objectives 1, 2, and 4. Section 3.2.3: Removed text and Table 4. Specified "Not applicable. Exploratory endpoints are not assessed for the abbreviated CSR.". Section 4.1: Removed the PK analysis set. Section 4.2: Removed reference to the PK analysis set. Section 5.1: Renumbered Table 5 as Table 4. Section 5.2: Replaced existing text with "Not applicable. Given the study terminated prematurely, primary and key secondary endpoints are not tested.". Section 6.1.1.1: Removed text "All TLFs are formatted and numbered according to the latest version of Biohaven Standard Outputs for CSRs.". Removed reference to the PK analysis set. Section 6.1.3: Removed references to sensitivity analyses. Section 6.2.1: Removed reference to the PK analysis, frequency table of inclusion/exclusion from the efficacy analysis set, and listing of subjects excluded from the efficacy analysis set. Section 6.2.2: Removed the frequency table of accrual over time. Section 6.2.3.2: Removed frequency table of randomization to treatment. Section 6.2.3.3: Renumbered section as 6.2.3.2. Section 6.2.5: Removed baseline characteristics tables for (1) efficacy analysis set and (2) full analysis set excluded from the efficacy analysis set. Removed the frequency table of randomization age group. Section 6.2.5.1: Removed NEWS2, ECGs, and chest x-ray results from the table of baseline efficacy and safety findings. Section 6.2.6.1: Removed first sentence after last bullet. Removed tables by subgroup level and overall for all subgroups of interest and the listing of study drug. Section 6.2.6.2: Added parameters to the listing of treatment compliance. Section 6.3: Specified that "Given that the study terminated prematurely and failed to achieve its planned sample size, all efficacy analyses are descriptive without treatment group comparisons.". Section 6.3.1: Specified there are 3 key secondary endpoints. Removed subsection on randomized age group. Modified Table 6 as follows: renumbered as Table 5; retitled as "Primary and Key Secondary Efficacy Endpoints and Analyses"; CCI [redacted] Section 6.3.1.1: Removed references to randomized age group. Added 95% CI for mean based on the t-distribution to the summary table of values and changes from baseline. Removed subsection "Treatment Group Comparisons". Section 6.3.1.2: Removed references to randomized age group and stratification. Removed subsection "Treatment Group Comparisons". Section 6.3.1.3: Removed. Section 6.3.2: Moved text from Section 6.3.2.1 here and references to "main". Removed Sections 6.3.2.2 through 6.3.2.4. Corrected reference from Section 6.4.4 to 6.4.3. Removed tables of treatment group comparisons. Specified that the "Ongoing and not reached the visit" category exists only before the final database lock in the frequency table. Section 6.3.3: Removed text about the Holm procedure. Section 6.3.3.1, 6.3.3.2, and 6.3.3.3: Removed treatment group comparisons. Removed sensitivity analyses and references to "main". Sections 6.3.3.4 CCI [redacted] Removed.

	Section 6.4: Removed ECGs and arterial blood gas as safety measures. Removed pretreatment safety tables for the enrolled analysis set by overall. Section 6.4.1: Removed listings of SAEs and AEs leading to study drug discontinuation. Section 6.4.1.2: Modified the contents of AE overview tables. Removed AE overview frequency tables for the following safety analysis periods and analysis sets: on-treatment for the safety analysis set by subgroup level and overall for all subgroups of interest; and on-study for the safety analysis set. Section 6.4.1.3: • Removed the following frequency tables: endpoints marked with "*" by subgroup level and overall for all subgroups of interest; pretreatment AEs for the enrolled analysis set; TEAEs occurring in ≥ 2% of subjects on zavegepant and greater than placebo after rounding for the safety analysis set; TEAEs by relationship to study drug for the safety analysis set; on-study AEs for the safety analysis set. • Added frequency tables of non-SAEs occurring with ≥ 5% frequency to support clinicaltrials.gov. Section 6.4.1.2: Removed all frequency tables except worst laboratory test abnormalities for the following safety analysis periods and analysis sets: on-treatment for the safety analysis set; and follow-up for the follow-up safety analysis set. Section 6.4.2: Removed listings of pregnancy test results and LFT values and ratios to ULN. Section 6.4.2.2: Removed on-study frequency tables and the eDISH scatter plot. Section 6.4.2.3: Removed the on-study frequency table and references to randomized age group. Combined results across the on-treatment and follow-up safety analysis periods in 1 table. Section 6.4.2.4: Removed. Section 6.4.3: Moved text from Section 6.4.3.2 here. Removed the listing of vital signs and physical measurements. Referred to the Core SAP for TLF contents. Sections 6.4.3.1 and 6.4.3.2: Removed. Sections 6.4.4, 6.4.7, and 6.4.9: Removed. Section 6.4.5: Renumbered as Section 6.4.4. Removed the on-study frequency table of chest x-ray results for the safety analysis set. Section 6.4.6: Renumbered as Section 6.4.5. Section 6.4.8: Renumbered as Section 6.4.6. Removed the listing of course of care. Section 6.4.10: Renumbered as Section 6.4.7. Section 7.1: Removed initial hospitalization discharge date and initial hospitalization return date. Section 7.3: Renumbered Table 8 as Table 6. Section 7.3.2: Retitled as "Safety Measurements in Analysis Visit Windows". Section 8: Modified text as: "The final CSR was planned after the last planned analysis (after the last subject reached Day 60). A full CSR will not be produced due to premature study termination. The abbreviated CSR is produced after database lock in 4Q2022. All analyses described in this SAP are included."

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CPAP	Continuous positive airway pressure
CSR	Clinical study report
CTCAE	Common Technical Criteria for Adverse Events
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
ECMO	Extra corporeal membrane oxygenation
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOFU	End of follow-up
EOT	End of treatment
FiO_2	Fraction of inspired oxygen
ICH	International Conference on Harmonization
ICU	Intensive care unit
IL	Interleukin
IN	Intranasal
IWRS	Interactive Web Response System
LFT	Liver function test
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of diet in renal disease
NC=F	Non-Completer = Failure
NEWS2	National Early Warning Score 2
NSAID	Non-steroidal anti-inflammatory drug

OP=F	Ongoing Procedure = Failure
PT	Preferred Term
PK	Pharmacokinetic
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Serious acute respiratory syndrome coronavirus-2
SD	Standard deviation
SI	Systeme Internationale
SOC	System organ class
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral capillary oxygen saturation measured by pulse oximeter
SpO_2/FiO_2	Ratio of pulse oximeter-measured oxygen saturation to fraction of inspired oxygen
TEAE	Treatment-emergent adverse event
TBL	Total bilirubin
Th17	Type 17 helper cells
TLF	Table Listing Figure
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

1 BACKGROUND AND RATIONALE

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3500-203: Phase 2/3: Double-Blind Randomized, Placebo Controlled, Safety and Efficacy Trial of Zavegepant (BHV-3500) Intranasal (IN) for Hospitalized Patients with COVID-19 Requiring Supplemental Oxygen.

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). The SAP containing the analyses for the Data Monitoring Committee (DMC) is provided in a separate document.

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 4Q2022 due to low enrollment. As a result, an abbreviated CSR will be provided instead of a CSR. Thus, the SAP is being amended from Version 3.0 to 4.0 to reduce the number of TLFs for the abbreviated CSR.

1.1 Research Hypothesis

Zavegepant reduces and slows the progression of the disease and improves overall outcome of Coronavirus Disease 2019 (COVID-19) infection.

1.2 Schedule of Analyses

The following planned analyses will be conducted:

- First DMC analysis (after the first 25% of subjects reach Day 15); analyses will be performed by an unblinded statistician.
- Second DMC analysis (after the first 50% of subjects reach Day 15) including futility analysis; analyses will be performed by an unblinded statistician.
- First planned analysis (after the last subject reaches Day 29); the database will be locked and the entire study team will be unblinded.
- Last planned analysis (after the last subject reaches Day 60).

If the study is terminated prematurely, then only the last planned analysis will be conducted unblinded.

2 STUDY DESCRIPTION

2.1 Study Design

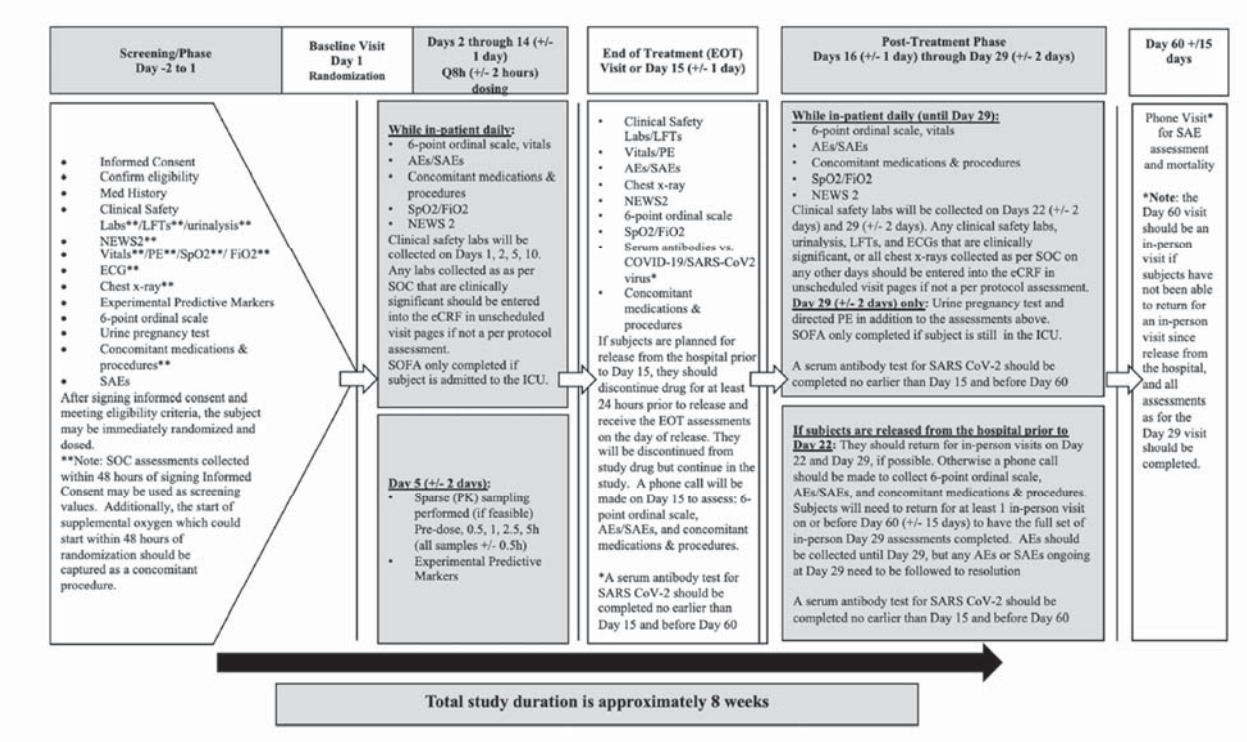
This is a double-blind, randomized, multicenter, inpatient (and post-discharge outpatient) evaluation of the safety and efficacy of zavegepant (BHV-3500) as compared to placebo in the

treatment of COVID-19 associated pulmonary disease. The study medications are zavegepant 10 mg or matching placebo, given as an intranasal (IN) dose every 8 hours for 14 days. After completion of treatment, subjects are followed to Day 60 during the post-treatment phase.

The study plans to randomize approximately 120 subjects in a 2:1 ratio across 2 treatment groups (zavegepant or matching placebo).

Figure 1 displays the study design.

Figure 1 Study Schematic



2.2 Treatment Assignment

Randomization is done through an IWRS that is accessed by the unblinded research pharmacists or their designees.

The randomization is stratified by age group (< 60, ≥ 60 years). The phrase "randomized age group" is used hereafter to denote the IWRS randomization age strata.

2.3 Blinding and Unblinding

The study is a double-blind study.

A pharmacokineticist, unblinded site monitor, unblinded site pharmacist, Biohaven Drug SupplyCoordinator and pharmacovigilance designees may be unblinded before the data are unblinded for the first planned DMC analysis.

For purposes of the DMC, periodic analyses are carried out by the unblinded biostatistics team that is independent and firewalled from the study team directly involved with the design, conduct and primary analysis of the trial.

Except as noted above, all other members of the team will remain blinded.

2.4 Protocol and Protocol Amendments

BHV3500-203 SAP Version 1.0 is based on BHV3500-203 Protocol Version 4.0 (12-Aug-2020).

BHV3500-203 SAP Version 2.0 is based on BHV3500-203 Protocol Version 6.0 (10-Nov-2020), which replaced the Hochberg procedure with the Holm procedure for testing the key secondary endpoints.

BHV3500-203 SAP Version 3.0 and 4.0 are based on BHV3500-203 Protocol Version 7.0 (11-May-2022), which (1) changed other (non-key) secondary efficacy objectives to exploratory efficacy objectives, and (2) modified the language for exploratory objective #10.

3 STUDY OBJECTIVES AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objective

To compare the efficacy of zavegepant (BHV-3500) to placebo, in subjects hospitalized with COVID-19 infection requiring supplemental oxygen, using a 6-point rating scale at Day 15.

3.1.2 Secondary Objectives

3.1.2.1 Key Secondary Objectives

1. To compare zavegepant to placebo on the proportion of subjects alive and off of oxygen at Day 29.
2. To compare zavegepant to placebo on the proportion of subjects requiring initiation of invasive mechanical ventilation, non-invasive ventilation or use of high flow oxygen devices through Day 29.
3. To compare zavegepant to placebo on the proportion of subjects admitted into an intensive care unit (ICU) through Day 29.

3.1.2.2 Other Secondary Objectives

1. To examine the safety of zavegepant, relative to placebo, as reflected by the number of: deaths; serious adverse events (SAEs;) severe adverse events (AEs); and Grade 3 or 4 laboratory test abnormalities.
2. To examine the safety of zavegepant, relative to placebo, as reflected by the incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infections through Day 29.

3. To examine the safety of zavegepant, relative to placebo, as reflected by the incidence of intranasal administration reactions through Day 29.
4. To examine the safety of zavegepant, relative to placebo, as reflected by the proportion of subjects who develop a significant loss of renal disease function, defined as at least 50% reduction in estimated glomerular filtration rate (eGFR) from baseline.

CCI [redacted]

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.

Population of Interest

The population of interest for this study is adult, male and female patients, with documented COVID-19 infection that requires hospitalization with supplemental oxygen or non-invasive mechanical ventilation. Subjects that are in immediate need of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) are excluded from the study and are not part of the population of interest. Protocol Section 5 "Population" provides a detailed description of inclusion and exclusion criteria for this study.

Intercurrent Events

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

Note that efficacy and safety data are still collected after premature study drug discontinuation and after hospitalization discharge during the post-treatment phase.

- 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.
- For safety objectives, study drug discontinuation is handled with 2 strategies:

- "While-on-treatment strategy", which is reflected in the "on-treatment" safety analyses.
- "Treatment policy strategy", which is reflected in select "on-study" safety analyses.

For all objectives, dose titration and use of other investigational therapies are not considered to be relevant intercurrent events. All objectives are assessed regardless of the use of another investigational medication during the course of treatment, or if a dose of investigational product has been titrated downward.

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

Data Sources for Endpoints

Six-point severity ratings are from 6-Point Ordinal Severity Rating Scale (6POSRS) electronic case report forms (eCRFs).

Procedures are from Concomitant Procedures eCRFs.

Respiratory rate, temperature, SpO_2, and FiO_2 are from Vital Signs eCRFs.

Deaths are determined from the following eCRFs: 6POSRS; AE/SAE; Screening/Double-Blind Subject Disposition; and Post-Treatment/Follow Up Disposition.

AEs (i.e., non-serious AEs or SAEs) are from AE/SAE eCRFs. This includes ICU admission.

Laboratory test results, including all exploratory biomarkers except CGRP plasma concentrations, are from laboratory test eCRFs (i.e., Clinical Safety Lab Testing, Liver Function Testing, Urinalysis Lab Testing, and Pregnancy Test).

3.2.1 Primary Objective Estimand

Table 1 presents the estimand for the primary objective.

Table 1 Primary Objective Estimand

Objective	**To evaluate the efficacy of zavegepant (BHV-3500) compared with placebo, in subjects hospitalized with COVID-19 infection requiring supplemental oxygen, using a six-point rating scale at Day 15**
Efficacy Endpoint	Mean 6POSRS rating at Day 15. Deaths through Day 15 from AE/SAE and subject disposition eCRFs are also taken into account.
Summary	Using the efficacy analysis set: • Descriptive statistics for observed data as both a continuous and categorical variable by treatment group
Intercurrent Events	Data included before and after study drug discontinuation: Treatment policy strategy

3.2.2 Secondary Objective Estimands

3.2.2.1 Key Secondary Objective Estimands

Table 2 presents the estimands for key secondary objectives.

Table 2 Key Secondary Objective Estimands

Objective 1	**To compare zavegepant to placebo on the proportion of subjects alive and off of oxygen at Day 29**
Efficacy Endpoint	Proportion of subjects who (1) have a 6POSRS rating of 5 or 6, (2) are alive, and (3) do not use supplemental oxygen as a procedure at Day 29
Summary	Using the efficacy analysis set: • Descriptive statistics for observed categorical data by treatment group
Intercurrent Events	• Death is part of the endpoint definition: Composite strategy • Data included before and after study drug discontinuation: Treatment policy strategy
Objective 2	**To compare zavegepant to placebo on the proportion of subjects requiring initiation of invasive mechanical ventilation, non-invasive ventilation or use of high-flow oxygen devices through Day 29**
Efficacy Endpoint	Proportion of subjects who (1) have a 6POSRS rating of 2 or 3, or (2) use ventilation or high-flow nasal cannula as a procedure on any day through Day 29
Summary	Using the efficacy analysis set: • Descriptive statistics for observed categorical data by treatment group
Intercurrent Events	Data included before and after study drug discontinuation: Treatment policy strategy
Objective 3	**To compare zavegepant to placebo on the proportion of subjects admitted into an intensive care unit (ICU) through Day 29**
Efficacy Endpoint	Proportion of subjects admitted into an ICU on any day through Day 29 from AE eCRFs
Summary	Using the efficacy analysis set: • Descriptive statistics for observed categorical data by treatment group
Intercurrent Events	Data included before and after study drug discontinuation: Treatment policy strategy

3.2.2.2 Other Secondary Objective Estimands

Table 3 presents the estimands for other secondary objectives.

Table 3 Other Secondary Objective Estimands

Objective 1	**To examine the safety of zavegepant, relative to placebo, as reflected by the number of: deaths; SAEs; severe AEs; and Grade 3 or 4 laboratory test abnormalities**
Safety Endpoint	Number of subjects with deaths, SAEs, severe AEs, and Grade 3 or 4 laboratory test abnormalities at any time. Grade 3 or 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria defined in the SAP.

Summary	Using the safety analysis set: • Number and percentage of subjects with these events or findings on treatment by treatment group
Intercurrent Events	Data included through study drug discontinuation ("on-treatment"): While-on-treatment strategy
Objective 2	**To examine the safety of zavegepant, relative to placebo, as reflected by the incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infections through Day 29**
Safety Endpoint	Number and percentage of subjects with severe or life-threatening bacterial, invasive fungal, or opportunistic infection AEs at any time through Day 29
Summary	Using the safety analysis set: • Number and percentage of subjects with intranasal administration reaction AEs on study through Day 29 by treatment group
Intercurrent Events	Data included before and after study drug discontinuation: Treatment policy strategy
Objective 3	**To examine the safety of zavegepant, relative to placebo, as reflected by the incidence of intranasal administration reactions through Day 29**
Safety Endpoint	Number and percentage of subjects with intranasal administration reaction AEs at any time through Day 29
Summary	Using the safety analysis set: • Number and percentage of subjects with intranasal administration reaction AEs on study through Day 29 by treatment group
Intercurrent Events	Data included before and after study drug discontinuation: Treatment policy strategy
Objective 4	**To examine the safety of zavegepant, relative to placebo, as reflected by the percentage of subjects who develop a significant loss of renal disease function defined as at least 50% reduction in eGFR from baseline**
Safety Endpoint	Proportion of subjects with ≥ 50% reduction in eGFR from baseline at any time from laboratory test eCRFs
Summary	Using the safety analysis set with nonmissing eGFR values at both baseline and ≥ 1 on-treatment time point: • Proportion of subjects with ≥ 50% reduction in eGFR from baseline on treatment by treatment group
Intercurrent Events	Data included through study drug discontinuation ("on-treatment"): While-on-treatment strategy

CCI [redacted]

[redacted]

4 ANALYSIS SETS, TREATMENT GROUPS, AND SUBGROUPS

4.1 Analysis Sets

The following analysis sets will be used in this this study:

- Enrolled: Subjects who sign informed consent and are assigned a subject identification number. This analysis set is used mainly to assess study population and in by-subject listings.

- Randomized: Subjects in the enrolled analysis set who receive a randomized treatment group assignment (zavegepant or placebo). This analysis set is used mainly to assess study population.
- Safety: Subjects in the enrolled analysis set who receive ≥ 1 dose of study drug (zavegepant or placebo). This analysis set is used to assess study population, exposure, and on-treatment 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.
- Efficacy: Subjects in the randomized analysis set who are randomized only once and receive ≥ 1 dose of study drug. This analysis set is used to assess study population and efficacy.
- Full: Subjects in the randomized or safety analysis set.

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

4.2 Treatment Groups

The 2 treatment groups are zavegepant and placebo.

The safety and follow-up analysis sets are assessed by as-treated treatment group (i.e., actual treatment received).

The full, randomized, and efficacy analysis sets are assessed by as-randomized treatment group.

The enrolled analysis set is assessed overall.

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

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

4.3 Subgroups

Not applicable.

5 SAMPLE SIZE, POWER, AND TYPE I ERROR

5.1 Sample Size and Power

This study plans to randomize 120 subjects in a 2 to 1 ratio, to zavegepant and placebo, respectively. Because our understanding of the course of the disease as measured by 6POSRS and the ability of the drug to alter that course, are limited, the sample size for this study was primarily based on what is typical for a Phase 2 study. Based on a limited set of encountered data, presented below, we believe the study may have roughly 90% power to detect an average improvement of 1 unit on the primary endpoint.

Just prior to the creation of the protocol, Biohaven informally gathered epidemiological data from local hospitals for 300 subjects tested for COVID-19. Table 4 shows the resulting estimated 6POSRS distribution.

Table 4 Estimated 6POSRS Distribution of 300 Subjects Tested for COVID-19 from Local Hospitals

Category	Description	N	%
1	Death	4	1.3%
2	Hospitalized, on invasive mechanical ventilation or ECMO	34	11.3%
3	Hospitalized, on non-invasive ventilation or high flow oxygen devices	30	10.0%
4	Hospitalized, requiring supplemental oxygen	20	6.7%
5	Hospitalized, not requiring supplemental oxygen	14	4.7%
6	Not hospitalized	198	66.0%

In this study, the subjects will have tested positive for COVID-19, have been admitted to a hospital, and will generally be in category 4 (hospitalized, requiring supplemental oxygen). The distribution of subjects after 14 days of treatment with either zavegepant or placebo is a matter of speculation. However, it does seem reasonable to discount the large number of subjects in category 6 (not hospitalized). These subjects, who were tested and sent home, would not be admitted into this study. If the category 6 subjects are not included in the calculations, then the distribution of the remaining 6POSRS data can be described as having a mean of 3.1 and a standard deviation (SD) of 1.1.

Based on the table, we speculate that after 14 days of treatment, the distribution of subjects on placebo may have a SD as high as 1.5. If zavegepant improves the response of subjects by an average of 1 unit over placebo, then this study will have roughly 90% power. This calculation is based on a t-test with sample sizes of 80 and 40 per treatment group, an alpha level of 0.05, and a common SD of 1.5.

5.2 Type I Error

Not applicable. Given the study terminated prematurely, primary and key secondary endpoints are not tested.

6 STATISTICAL ANALYSES

6.1 General

6.1.1 Programmed Output

A separate document contains the list of all TLFs, along with corresponding templates, attributes, and programming notes.

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

6.1.1.1 Tables

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

- Results for the enrolled analysis set is presented only overall, without treatment group.
- Results for select study population endpoints, pretreatment safety endpoints, and the full and follow-up safety analysis sets are presented by treatment group and overall.

6.1.1.2 By-subject Listings

In general, by-subject listings are sorted by randomization status (randomized, not randomized), site-subject ID, and additional sorting parameters specified in the Core SAP, this SAP, or the associated TLF document. Randomization status is not displayed.

By-subject listings display abbreviated treatment group (e.g., ZAV for zavegepant, PBO for placebo, and NRND for not randomized). All listings display the as-randomized treatment group.

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.

Summary statistics for continuous variables include n, mean, SD, median, Q1, Q3, minimum, and maximum.

All CIs are 2-sided with a 95% confidence level, unless specified otherwise.

6.1.3 Handling of Missing Data

For the primary endpoint, the analysis uses all available data under the missing at random (MAR) assumption, and subjects who died at an analysis visit have a 6POSRS rating of 1 ("death") used at the analysis visit and all analysis visits thereafter (see Section 6.3.2).

For the key secondary endpoints, the analysis uses the last available value (see Section 6.3.3).

6.2 Study Population

Results are presented by treatment group and overall, unless specified otherwise.

Refer to the Core SAP for TLF contents.

6.2.1 Analysis Sets

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

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

The by-subject administrative listing of randomization scheme and codes is provided for all randomization numbers and block numbers, even those not assigned to a subject. This listing is sorted by randomization number and block number, and displays the randomization number, block number, site-subject ID, treatment group, randomized age group, and randomization date.

6.2.2 Enrollment

Frequency tables of enrollment by (1) country and site and (2) age group are provided overall for the enrolled analysis set. The enrollment by country and site table also displays results for the full and safety analysis sets.

6.2.3 Subject Disposition

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

See Section 7.1 for derived dates.

6.2.3.1 Subject Disposition from Enrollment to Randomization

Results are based on the Screening/Double-Blind Subject Disposition eCRF.

The frequency table of subject disposition from enrollment to randomization is provided for the enrolled analysis set by overall, and displays the following categories:

- Randomized (i.e., nonmissing IWRS randomization date)
- Not randomized (i.e., missing IWRS randomization date)
    - Reasons for not randomized, including not reported. For subjects whose reason is inclusion/exclusion failure, the most relevant inclusion/exclusion criteria are also displayed as subcategories, including not reported.

The by-subject listing of subject disposition during the screening phase is provided for the enrolled analysis set, and includes the informed consent date, IWRS randomization date, last contact date, randomization status (yes, no), most relevant inclusion/exclusion criteria, and reason for not randomized with specified text for other. 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, and safety parameters".

6.2.3.2 Subject Disposition during the Double-blind Treatment Phase

Results are based on the Screening/Double-Blind Subject Disposition eCRF.

The frequency table of subject disposition during the double-blind treatment phase is provided for the safety analysis set by as-treated treatment group and overall, and displays the following categories:

- Completed 14 days of dosing (i.e., "yes" response to "Did the subject complete 14 days of dosing?")
- Did not complete 14 days of dosing (i.e., "no" response to "Did the subject complete 14 days of dosing?")
  - Reasons for not completing the dosing regimen, including not reported
- Ongoing 14-day dosing status (i.e., missing response to "Did the subject complete 14 days of dosing?") *
- Completed all visits in the treatment phase (i.e., "yes" response to "Did the subject complete all VISITS in the Treatment Phase (Days 1 to 14 +/-1)?")
- Did not complete all visits in the treatment phase (i.e., "no" response to "Did the subject complete all VISITS in the Treatment Phase (Days 1 to 14 +/-1)?")
  - Reasons for not completing all treatment phase visits, including not reported
- Ongoing treatment phase visit completion status (i.e., missing response to "Did the subject complete all VISITS in the Treatment Phase (Days 1 to 14 +/-1)?") *
- Completed the Day 15 visit (i.e., "yes" response to "Did the subject complete the Day 15 Visit"?)
- Did not complete the Day 15 visit (i.e., "no" response to "Did the subject complete the Day 15 Visit"?)
  - Reasons for not completing the Day 15 visit, including not reported
- Ongoing Day 15 visit completion status (i.e., missing response to "Did the subject complete the Day 15 Visit"?). *

At the first and final planned database locks, subjects in categories marked with "*" are instead displayed in the "not reported" subcategory of not completing the respective milestone.

The by-subject listing of subject disposition during the double-blind treatment phase is provided for the randomized analysis set, and displays the study drug start date/time, study drug end date/time, last contact date, dosing regimen completion status (yes, no), reason for not completing the dosing regimen with specified text for other, treatment phase visit completion status (yes, no), reason for not completing all visits with specified text for other, Day 15 visit completion status (yes, no), reason for not completing the Day 15 visit with specified text for other, and treatment phase completion/discontinuation date. A footnote describes the derivation of the last contact date (see Section 6.2.3.1).

6.2.3.3 Subject Disposition during the Follow-up Phase

Results are based on the Post-Treatment/Follow Up Disposition eCRF.

The frequency table of subject disposition during the follow-up phase is provided for the safety analysis set by as-treated treatment group and overall, and displays the following categories:

- Completed the Day 29 visit (i.e., "yes, in-person visit" or "yes, telephone visit" response to "Did the subject complete the Day 29 Visit"?)
  - Type of visit (i.e., in-person visit or telephone visit)
- Did not complete the Day 29 visit (i.e., "no" response to "Did the subject complete the Day 29 Visit"?)
  - Reasons for not completing the Day 29 visit, including not reported
- Ongoing Day 29 visit completion status (i.e., missing response to "Did the subject complete the Day 29 Visit"?). At the first and final planned database locks, subjects in this category are instead displayed in the "not reported" subcategory of not completing the Day 29 visit.
- Completed the Day 60 visit (i.e., "yes, in-person visit" or "yes, telephone visit" response to "Did the subject complete the Day 60 Follow-Up Visit"?)
  - Type of visit (i.e., in-person visit or telephone contact)
- Did not complete the Day 60 visit (i.e., "no" response to "Did the subject complete the Day 60 Follow-Up Visit"?)
  - Reasons for not completing the Day 60 visit, including not reported.
- Ongoing Day 60 visit completion status (i.e., missing response to "Did the subject complete the Day 60 Follow-Up Visit"?). At the final planned database lock, subjects in this category are instead displayed in the "not reported" subcategory of not completing the Day 60 visit.

The by-subject listing of subject disposition during the follow-up phase is provided for the safety analysis set, and displays the last contact date, Day 29 visit completion status (yes, no), reason for not completing the Day 29 visit with specified text for other, Day 60 visit completion status (yes, no), reason for not completing the Day 60 visit with specified text for other, and study completion/discontinuation date. A footnote describes the derivation of the last contact date (see Section 6.2.3.1).

6.2.4 Protocol Deviations

Results are based on the Protocol Violations and Deviations eCRF.

The frequency table of significant protocol deviations is provided by as-randomized treatment group and overall for the full analysis set, and displays the following deviation type categories:

- Eligibility criteria
- Incorrect stratification

- Informed consent
- Other
- Procedure performed out of window
- Procedure not performed
- Prohibited concomitant medications
- Regulatory
- SAE reporting
- Study medication not taken according to schedule
- Visit schedule.

Deviation types are presented in descending order of overall frequency.

The by-subject listing of significant protocol deviations is provided for the enrolled analysis set. This includes date of deviation, type including other specify, and description, which are additional sorting variables.

Significant protocol deviations are defined as those with a "yes" response to the question "Is this protocol deviation significant?".

6.2.5 Baseline Characteristics

Baseline characteristics include (1) demographics and other relevant baseline characteristics, (2) COVID-19 history, (3) medical history, and (4) non-study prior medications.

Tables of baseline characteristics (1) through (4) are provided for the safety analysis set by as-treated treatment group and overall to support safety.

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 ("last" is determined by the measurement date/time and subject visit form ID).

The following by-subject listings are provided for the enrolled analysis set: demographics; COVID-19 history (see Section 6.2.5.2); and medical history.

6.2.5.1 Demographics and Other Relevant Baseline Characteristics

Demographics

Demographics include the categorical parameters of sex, race, ethnicity, and country, and the following:

- Age at informed consent (years), also categorized as < 60 or ≥ 60 and < 65 or ≥ 65
- Randomized age group (< 60, ≥ 60 years)

- Age at randomization (years), categorized as < 60, ≥ 60. Age at randomization is calculated using the IWRS randomization date as the reference date.

Refer to the Core SAP for the table of demographics and deriving age at a reference date.

Baseline Efficacy and Safety Findings

The table of baseline efficacy and safety findings includes the following parameters summarized descriptively as categorical or continuous variables:

- 6POSRS rating, also categorized as 1 through 6, from the 6POSRS eCRF
- Vital signs and physical measurements: temperature, heart rate, respiratory rate, SpO2, FiO2, SpO2/FiO2 ratio, systolic blood pressure, diastolic blood pressure, height, weight, body mass index (BMI). BMI is also categorized as < 25, ≥ 25 to < 30, ≥ 30 kg/m^2. See Section 6.4.3.

6.2.5.2 COVID-19 History

Results are based on the Medical History eCRF.

The table of COVID-19 history includes the following parameters summarized descriptively as categorical or continuous variables:

- Time from onset of initial COVID-19 symptoms to informed consent (days), derived as (informed consent date – onset date of initial COVID-19 symptoms)
- Time from onset of initial COVID-19 symptoms to study drug start (days), derived as (study drug start date – onset date of initial COVID-19 symptoms). This is defined only for the safety and efficacy analysis sets.
- Time from COVID-19 confirmation to informed consent (days), derived as (informed consent date – date COVID-19 confirmed by laboratory test)
- Time from initial hospitalization to informed consent (days), derived as (informed consent date – initial hospitalization date)
- Reason for hospitalization (e.g., difficulty breathing, shortness of breath)
- Clinical assessment of baseline COVID-19 severity (e.g., SARS-CoV-2 Infection without symptoms, mild COVID-19).

6.2.5.3 Medical History

The frequency table of medical history is provided by SOC and PT, and displayed in descending order of overall frequency within SOC and PT.

6.2.5.4 Non-study Prior Medications

The frequency table of non-study current medications is provided by therapeutic class and preferred name. Medications are displayed in descending order of overall frequency within therapeutic class and preferred name. See Section 6.2.6.3.

6.2.6 Exposure

Exposure is presented by as-treated treatment group and overall.

6.2.6.1 Study Therapy

The table of double-blind study drug exposure is provided for the safety analysis set, and summarizes the following parameters as continuous or categorical variables:

- Time on study drug (days), derived as (study drug end date – study drug start date + 1)
- Time on study drug categories: ≤ 5, 6 to 10, 11 to 14, ≥ 15 days
- Time on study drug (hours), derived as the number of hours between the study drug start and end date/times
- Cumulative exposure (sprays), derived by summing number of sprays administered across records with complete study drug dates
- Total exposure (sprays) summed across all subjects, derived by summing the cumulative exposure across all subjects
- Time on study (days), derived as (last contact date – study drug start date + 1)
- Time on study categories: ≤ 5, 6 to 10, 11 to 15, 16 to 20, 21 to 30, 31 to 40, 41 to 50, 51 to 60, ≥ 61 days.

See Section 7.1 for derived dates.

6.2.6.2 Treatment Compliance

The table of treatment compliance is provided for the safety analysis set, and summarizes the following parameters as continuous or categorical variables:

- On-treatment compliance (%), derived as 100 × (cumulative exposure/actual exposure), where actual exposure = [(time on study drug in hours / 8) truncated to an integer] + 1. See Section 6.2.6.1 for cumulative exposure.
- On-treatment compliance categories: < 80%, ≥ 80% to < 90%, ≥ 90% to 100%, > 100%
- 14-day treatment compliance (%), derived as 100 × (cumulative exposure/42)
- 14-day treatment compliance categories: < 80%, ≥ 80% to < 90%, ≥ 90% to 100%, > 100%
- Study drug gap ≥ 1 day, defined as ≥ 1 day on which no study drug spray is administered between the study drug start and end dates
- Incorrect study drug administered for ≥ 1 spray. These are subjects randomized to zavegepant who receive ≥ 1 spray of placebo, and subjects randomized to placebo who receive ≥ 1 spray of zavegepant. Carton numbers from the Study Medication Administration Log eCRF are compared with the unblinded container file in order to determine incorrect study drug.

- Incorrect study drug administered for the entire treatment period, defined as as-treated treatment group not equal to as-randomized treatment group.

The by-subject listing of treatment compliance is provided for the safety analysis set, and displays results for treatment compliance parameters in separate columns: time on study drug (days); cumulative exposure (sprays); time on study (days); percentage for on-treatment compliance and 14-day treatment count compliance; flags for the other parameters ("Y" or missing).

6.2.6.3 Concomitant and Follow-up Non-study Medications

Frequency tables of the following non-study medications are provided:

- Concomitant medications for the safety analysis set by treatment group
- Follow-up medications for the follow-up safety analysis set by treatment group and overall.

Medications are displayed in descending order of zavegepant frequency for the safety analysis set. Medications are displayed in descending order of overall frequency within therapeutic class and preferred name for the follow-up analysis set.

The by-subject listing of non-study medications is provided the enrolled analysis set. Medication types are identified.

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

6.3 Efficacy

Efficacy analyses are based on the efficacy analysis set by as-randomized treatment group only. Given that the study terminated prematurely and failed to achieve its planned sample size, all efficacy analyses are descriptive without treatment group comparisons.

6.3.1 Efficacy Overview

General Organization of Efficacy Analyses

There is 1 primary efficacy endpoint and 3 key secondary efficacy endpoints. Although numerous, these endpoints have structural similarities and can be grouped into analysis types, as shown in Table 5. The column labeled "Variable Type" indicates the nature of the dependent variable as continuous or binary.

Analysis Periods

Measurements are slotted into analysis periods (pretreatment, on-study) based on "measurement dates", which are measurement or assessment dates.

The phrase "Day *X*" denotes the Day *X* analysis visit window, where *X* = 5, 10, 15, 22, 29, and 60 (see Section 7.3).

For a given parameter and measurement date, the following phrases are defined:

- "Measurement at Day *X*" is defined as the lower bound of the Day *X* analysis visit window ≤ study day of the measurement date ≤ upper bound of the Day *X* analysis visit window.
- "Measurement through Day *X*" is defined as the study day of the measurement date ≤ upper bound of the Day *X* analysis visit window.
- "Measurement before Day *X*" is defined as the study day of the measurement date < lower bound of the Day *X* analysis visit window.
- "Missing measurement at Day *X"* is defined as all missing parameter values in the Day *X* analysis visit window.

See Section 7.3 for study days.

Study discontinuation before Day *X* is defined as (study discontinuation date – study drug start date + 1) < lower bound of the Day *X* analysis visit window.

Death from All Sources

Select endpoints take death from all sources into account, as determined by a nonmissing death date defined in Section 7.1.

For select endpoints based on 6POSRS ratings, subjects who died at an analysis visit have a 6POSRS rating of 1 ("death") used at the analysis visit, all analysis visits thereafter, EOT (if EOT 6POSRS rating date ≥ death date), and EOS, regardless of the observed 6POSRS data.

This data imputation method is applied before any other missing data are handled, such as imputing data with the last on-study value before the analysis visit or excluding subjects with missing data at the analysis visit. See Section 6.4.1.1 for the definition of death at an analysis visit.

Examples:

- Last study drug on study day 5, last 6POSRS rating of 1 on study day 6, and death on study day 6: 6POSRS rating of 1 is used at Days 5, 10, 15, 22, 29, 60, EOT, and EOS.
- Last 6POSRS rating of 5 on study day 4, last study drug on day 5, and death on study day 10: 6POSRS rating of 1 is used at Days 10, 15, 22, 29, 60, and EOS.
- Last 6POSRS rating of 2 on study day 15, last study drug on study day 15, and death on study day 16: 6POSRS rating of 1 is used at Days 15, 22, 29, 60, and EOS.
- Last 6POSRS rating of 2 on study day 15, last study drug on study day 15, and death on study day 18: 6POSRS rating of 1 is used at Days 22, 29, 60, and EOS.

Table 5 Primary and Key Secondary Efficacy Endpoints and Analyses

Index	Description	Variable Type	Source eCRF	On-study Data
Primary Efficacy Endpoint				
P01	Mean 6POSRS rating at Day 15	Continuous	6POSRS	Day 5
Key Secondary Efficacy Endpoints				
S01	Proportion of subjects alive and off oxygen at Day 29	Binary	6POSRS and Concomitant Procedures	Day 29
S02	Proportion of subjects requiring invasive mechanical ventilation, non-invasive ventilation, or use of high-flow nasal cannula through Day 29	Binary	6POSRS and Concomitant Procedures	Through Day 29
S03	Proportion of subjects admitted into an ICU through Day 29	Binary	AE/SAE	Through Day 29

The following by-subject listings of are provided for the enrolled analysis set, unless specified otherwise:

- Primary and key secondary efficacy endpoints for the randomized analysis set, including the following: 6POSRS rating at Day 15 for the main analysis; response/failure status (yes, no) for the main analysis for each key secondary endpoint; reasons for exclusion from the efficacy analysis set (see Section 6.2.1)
- 6POSRS assessments from the 6POSRS eCRF.

6.3.1.1 Continuous Efficacy Endpoints

Measurements are slotted into analysis visits as described in Section 7.3.1.

The table of summary statistics for parameter values and changes from baseline (including 95% CI for the mean based on a t-distribution) is provided at select time points by treatment group.

6.3.1.2 Binary Efficacy Endpoints

Measurements are slotted into analysis visits as described in Section 7.3.1, unless specified otherwise.

"Positive" endpoints such as alive and off oxygen, are described using response rates, i.e., "n/N" and percentage, where "n" denotes number of subjects meeting the positive endpoint criteria.

"Negative" endpoints such as admission into an ICU, are described using failure rates, i.e., "n/N" and percentage, where "n" denotes number of subjects meeting the negative endpoint criteria.

The table of response (or failure) rates and 95% exact Clopper-Pearson CIs is provided by treatment group.

6.3.2 Primary Efficacy Endpoint: 6POSRS Rating at Day 15

First, 6POSRS ratings on study are slotted into analysis visit windows and multiple values are handled (see Section 7.3.1). Next, death from all sources is taken into account as per Section 6.3 for all analyses described below.

All estimands are based on a treatment policy strategy that ignores premature study drug discontinuation.

All available data are used, after taking death from all sources into account.

The following 2 tables are produced:

- 6OSPRS rating and change from baseline as descriptive continuous variables over time at baseline, all analysis visits, EOT, and EOS (see Section 6.3.1.1).
- 6POSRS rating as a descriptive categorical variable over time at baseline, all analysis visits, EOT, and EOS. At each time point, the number and percentage of subjects in the following categories are presented:
  - Number of subjects with data. 6POSRS ratings 1 to 6 are presented as subcategories.
  - Number of subjects with missing data. The following subcategories are presented only at analysis visits:
    - Study discontinuation before the visit: study discontinuation date is not missing and last contact day (i.e., last contact date – study drug start date + 1) < lower bound of the analysis visit window
    - Ongoing and not reached the visit: study discontinuation date is missing and last contact day < lower bound of the analysis visit window. This category exists only before the final database lock.
    - Reached the visit: last contact day ≥ lower bound of the analysis visit window.

6.3.3 Key Secondary Efficacy Endpoints

See Table 5 for eCRF data sources for endpoints.

All estimands are based on a treatment policy strategy that ignores premature study drug discontinuation.

6.3.3.1 S01: Proportion of Subjects Alive and Off of Oxygen at Day 29

Alive and off oxygen (i.e., response) at Day 29 is defined as meeting all the following criteria:

- Alive at Day 29 (see Section 6.4.1.1)
- 6POSRS rating of 5 or 6 at Day 29. First, the 6POSRS rating at Day 29 is selected using methods described in Section 7.3.1. Next, death from all sources is taken into account (see Section 6.3). Finally, missing data at Day 29 are handled using methods described below.

- No use of supplemental oxygen as a procedure at Day 29 (see Sections 9.1 and 9.1.5). If the 6POSRS rating at Day 29 is observed (i.e., not missing and not imputed) as determined from the previous step, then the day of the observed 6POSRS rating cannot be a procedure day of supplemental oxygen use. Otherwise, there cannot be a procedure day of supplemental oxygen use at Day 29.

Response is assessed descriptively as a binary endpoint. Results are provided according to Section 6.3.1.2.

Subjects with missing 6POSRS rating at Day 29 have the last on-study 6POSRS rating before Day 29 used. In addition, subjects with ≥ 1 procedure day of supplemental oxygen use before Day 29 for an ongoing procedure are considered failures (i.e., not alive or not off of oxygen at Day 29; Ongoing Procedure = Failure [OP=F]; see Sections 9.1 and 9.1.5).

6.3.3.2 S02: Proportion of Subjects Requiring Initiation of Invasive Mechanical Ventilation, Non-invasive Ventilation, or a High-flow Nasal Cannula through Day 29

Requiring initiation of invasive mechanical ventilation, non-invasive ventilation or use of high flow oxygen devices (i.e., failure) through Day 29 is defined as either (1) any 6POSRS rating of 2 or 3 from the 6POSRS eCRF at any time on study through Day 29, or (2) ≥ 1 procedure day of ventilation or high-flow nasal cannula use on study through Day 29 (see Sections 9.1 and 9.1.4).

Failure is assessed descriptively as a binary endpoint. Results are provided according to Section 6.3.1.2.

Subjects with missing 6POSRS rating at Day 29 have all available on-study 6POSRS ratings before Day 29 used.

6.3.3.3 S03: Proportion of Subjects Admitted into an ICU through Day 29

Admission into an ICU through Day 29 (i.e., failure) through Day 29 is defined as ≥ 1 intensive care AE day on study through Day 29 (see Section 9.3).

Failure is assessed descriptively as a binary endpoint. Results are provided according to Section 6.3.1.2.

Subjects who discontinued the study before Day 29 have all available on-study AEs before Day 29 used.

6.4 Safety

Safety measures include AEs, laboratory tests, vital signs, physical measurements, chest x-rays, procedures, and course of care.

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

- Pretreatment for the safety analysis set by as-treated treatment group (i.e., the actual treatment received) and overall
- On-treatment for the safety analysis set by as-treated treatment group
- Follow-up for the follow-up safety analysis set by as-treated treatment group and overall
- On-study for the safety analysis set by as-treated treatment group.

Measurements are slotted into analysis periods (pretreatment, on-study, on-treatment safety, follow-up safety). Refer to the Core SAP for details about slotting AEs versus findings.

The phrase "through Day *X*" denotes (measurement date – study drug start date + 1) ≤ upper bound of the Day *X* analysis visit window.

6.4.1 Adverse Events

Refer to the Core SAP for the following: AE start and end date imputation; rules for counting and rounding in frequency tables; definitions of treatment-emergent adverse events (TEAEs), AEs related to study drug, and AEs of special interest; and TLF contents.

There are 3 types of emergent AEs:

- TEAEs are those that developed, worsened, or became serious during the on-treatment safety analysis period relative to the pretreatment analysis period.
- On-study emergent AEs are those that developed, worsened, or became serious during the on-study analysis period relative to the pretreatment analysis period.
- Follow-up emergent AEs are those that developed, worsened, or became serious during the follow-up safety analysis period relative to the pretreatment and on-treatment safety analysis periods combined.

Refer to the Core SAP for additional details about TEAEs that should be applied analogously to the other 2 types of emergent AEs.

In tables by SOC and PT that display an "Overall" treatment group column, AEs are displayed in descending order of overall frequency within SOC and PT. Otherwise, AEs are displayed in descending order of zavegepant frequency within SOC and and PT.

By-subject listings are provided for the enrolled analysis set for AEs (i.e., both non-SAEs and SAEs) and deaths.

6.4.1.1 Deaths

The frequency table of deaths is provided on study for the safety analysis set as the number and percentage of subjects who died on Days 5, 10, 15, 22, 29, died on or before Days 5, 10, 15, 22, 29, and overall.

Death on Day *X* is defined as lower bound of the Day *X* analysis visit window ≤ death day (i.e., death date – study drug start date + 1) ≤ upper bound of the Day *X* analysis visit window.

Death on or before Day *X* is defined as death day ≤ upper bound of the Day *X* analysis visit window.

Alive at Day *X* is defined as missing death date or death day > upper bound of the Day *X* analysis visit window.

Note that deaths are slotted to analysis periods according to death date/time (see Section 7.1).

Deaths are identified from any of the following 4 eCRF sources:

- 6POSRS eCRF with any of the following: Subject status of death; complete or partially complete death date.
- AE/SAE eCRF with any of the following: PT or reported term of "death"; outcome of "fatal"; SAE criterion of "death"; "yes" response to the "Did the death occur after withdrawal of care?" question.
- Screening/Double-Blind Subject Disposition eCRF: Death as reason for not completing the dosing regimen, all treatment phase visits, or Day 15 visit (see Section 6.2.3.2).
- Post-Treatment/Follow Up Disposition eCRF: Death as reason for not completing the Day 29 or Day 60 visit (see Section 6.2.3.3).

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

Results support Other Secondary Endpoint S01.

6.4.1.2 AE Overview

An AE overview frequency table displays the following categories without SOC and PT:

- AE
- Emergent AE
- Mild emergent AE
- Moderate emergent AE
- Severe emergent AE
- Emergent AE related to study drug
- SAE
- AE leading to study drug discontinuation
- Death (see Section 6.4.1.1).

Emergent applies only to the on-treatment safety, follow-up safety, and on-study analysis periods.

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

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

6.4.1.3 Adverse Events by SOC and PT

Pretreatment AEs

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

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

On-treatment AEs

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

- AEs by intensity
- Non-SAEs occurring with ≥ 5% frequency in any treatment group (supports clinicaltrials.gov)
- SAEs
- TEAEs by intensity
- TEAEs related to study drug by intensity
- AEs leading to study drug discontinuation.

Results support Other Secondary Endpoint S01.

Follow-up AEs

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

- AEs by intensity
- Non-SAEs occurring with ≥ 5% frequency overall (supports clinicaltrials.gov)
- SAEs

- Emergent AEs by intensity.

On-study AEs through Day 29

Frequency tables of on-study AEs through Day 29 are provided by SOC and PT for the safety analysis set and the following endpoints:

- Emergent local irritation AEs by intensity. Refer to the Core SAP. Results support Other Secondary Endpoint S02.
- Emergent, severe or life-threatening bacterial, invasive fungal, or opportunistic infection AEs by intensity. PTs are identified by the Biohaven medical lead or designee from reviewing a listing of unique, severe, life-threatening PTs from the "Infections and Infestations" SOC. AEs must have either (1) severe intensity or (2) an SAE criterion of life-threatening or death. Results support Other Secondary Endpoint S03.

AEs during the Entire Study

The frequency table of AEs leading to study drug discontinuation during the entire study (i.e., pretreatment and on-study analysis periods combined) is provided by SOC and PT for the safety analysis set.

6.4.2 Laboratory Tests

Laboratory tests are analyzed using local laboratory test results reported on Clinical Safety Lab Testing, Liver Function Testing, Urinalysis Lab Testing, and Pregnancy Test eCRFs.

TLFs present results in both SI (Systeme Internationale) and United States (US) unit systems, if applicable.

Laboratory tests are collected at the following visits:

- Hematology and serum chemistry (excluding tests listed below): Screening, end of treatment, and on days 1, 2, 5, 10, 15, 22, 29, and 60.
- Liver function tests (LFTs): Screening, end of treatment, and on day 15. These include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, and indirect bilirubin.
- Urinalysis: Screening.

If laboratory tests are collected as per standard or care on any other days from 1 through 29 and are clinically significant, then results are reported at unscheduled visits.

Laboratory test groups of clinical interest for analyses are hematology and serum chemistry (which includes LFTs). Clinically significant laboratory abnormalities are identified as grade 3 to 4 laboratory test results. Refer to the Core SAP for laboratory tests of clinical interest for analyses (including identification of those with toxicity grades) and TLF contents.

eGFR is derived using the modification of diet in renal disease (MDRD) formula as specified in the Core SAP. eGFR data from the Clinical Safety Lab Testing eCRF are not used in analyses described in the proceeding subsections.

By-subject listings of the following select laboratory test groups are provided for the enrolled analysis set: hematology; serum chemistry, including LFTs and eGFR derived using the MDRD formula; and urinalysis (US units only). Listings display clinically significant status (yes, no) from the eCRFs and toxicity grades, as applicable.

6.4.2.1 Laboratory Test Abnormalities

Results support Secondary Endpoint S21.

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

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

6.4.2.2 Liver Function Test Elevations

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

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

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

LFT ULN Shifts from Baseline to Worst Elevation

The frequency table of LFT ULN shifts from baseline to the worst (highest) LFT elevation on treatment is provided for the safety analysis set.

6.4.2.3 Significant Loss of Renal Function

Significant loss of renal function is defined as ≥ 50% reduction in eGFR. The frequency table of ≥ 50% reduction in eGFR from baseline by safety analysis period is provided for the safety analysis set and displays the following categories:

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

Percentages are based on the number of subjects with nonmissing eGFR values at both baseline and ≥ 1 time point in the safety analysis period.

Results support Other Secondary Endpoint S04.

6.4.3 Vital Signs and Physical Measurements

Vital signs and physical measurements are from Vital Signs eCRFs.

Vital signs include temperature (C), heart rate (beats per minute), respiratory rate (breaths per minute), SpO_2 (%), FiO_2, SpO_2/FiO_2 ratio, systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). SpO_2/FiO_2 ratio is a derived continuous variable, and is considered to be "collected" as an integer in tables of summary statistics. Vitals signs are collected at screening, baseline, daily while the subject is in the hospital, and after hospital discharge on days 22, 29, and 60.

Physical measurements include height (cm), weight (kg), and BMI (kg/m^2). BMI is derived as (weight in kg)/(baseline height in $m)^2$, and is considered to be "collected" to 1 decimal place in tables of summary statistics. Physical measurements are collected at screening, and on days 22 and 29.

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

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

Categories also include the following:

- SpO_2: < 90% and < 95%.
- SpO_2/FiO_2 ratio: ≤ 200, ≤ 300, and ≤ 400.

Refer to the Core SAP for TLF contents.

6.4.4 Chest X-rays

Chest x-rays are from Chest X-ray eCRFs, and are taken at screening, day 15, and EOT.

The by-subject listing of chest x-rays is provided for the enrolled analysis set.

6.4.5 Procedures

Procedures are from Concomitant Procedures eCRFs, unless specified otherwise.

The frequency table of on-study procedures is provided for the safety analysis set, and displays the following procedure categories:

- Supplemental oxygen use, defined as use of ventilation, low-flow nasal cannula, or high-flow nasal cannula (see Section 9.1.5)
- Ventilation use, defined as use of invasive mechanical ventilation or non-invasive ventilation (see Section 9.1.2)

- Invasive mechanical ventilation use (see Section 9.1.1). Individual procedures are displayed alphabetically as subcategories.
- Non-invasive ventilation use (see Section 9.1.2). Individual procedures are displayed alphabetically as subcategories.
- Low-flow or high-flow nasal cannula use (see Section 9.1.3). Individual procedures are displayed alphabetically as subcategories.
- Procedures other than supplemental oxygen use. Individual procedures are displayed alphabetically as subcategories. MedDRA PTs corresponding to "other" procedures are also displayed alphabetically as subcategories of "other".

For subjects who used and were removed from invasive mechanical ventilation on study, the frequency table of reasons for being removed from the ventilator (e.g., improved/no longer needed, clinical deterioration) is provided from Subject Journey eCRFs, including not reported. Subject journey assessment dates must be on study. If a subject has multiple reasons, then all reasons are provided. Use and removal from invasive mechanical ventilation on study is defined as ≥ 1 procedure day of invasive mechanical ventilation on study for a procedure that is not ongoing.

Procedures are slotted into analysis periods according to both imputed procedure start and imputed procedure end dates (see Sections 7.1 and 9.2). An ongoing procedure is defined as a procedure with a "yes" response to being ongoing.

The by-subject listing of procedures is provided for the enrolled analysis set, and includes analysis period (pretreatment, on-treatment safety, follow-up safety).

The by-subject listing of subject journey is provided for the enrolled analysis set from the Subject Journey eCRF.

6.4.6 Course of Care

Course of care is collected only at the end of the study from the Course of Care eCRF.

The frequency table of course of care is provided for the safety analysis set, and displays the following categories:

- Progress to acute respiratory distress syndrome (yes, no). For subjects with a "yes" response, supportive measures (e.g., proning, paralytics) are displayed as subcategories, with percentages based on the subset.
- Standard of care measures (e.g., contact and airborne precautions, airborne infection isolation room)
- Care decisions made based on resource limitation (yes, no).

Percentages are based on the number of subjects with nonmissing course of care data.

6.4.7 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 on treatment or during follow-up for the safety analysis set with as-treated treatment group of zavegepant
- AE leading to study drug discontinuation in any safety analysis period for the safety analysis set with as-treated treatment group of zavegepant
- Event of special interest on treatment for the safety analysis set with as-treated treatment group of zavegepant:
  - ALT or AST > 3x ULN
  - ALT or AST > 3x ULN concurrent with TBL > 2x ULN
  - ALP or TBL > 2x ULN
  - Select hepatic-related AE, i.e., PT containing cirrhosis, hepatic failure, hepatitis, jaundice, or liver failure
  - TEAE of local irritation with severe intensity
  - Suicidality AE.

Refer to the Core SAP for additional details.

7 CONVENTIONS

7.1 Derived Dates

- Study drug start date/time: Earliest nonmissing study drug dose date/time from the Study Medication Administration eCRF with status of "administered". This is an analysis period reference date.
- Study drug end date/time: Latest nonmissing study drug dose date/time from the Study Medication Administration eCRF with status of "administered".
- Study drug last date/time:
  - Before the first planned database lock: Study drug end date/time derived only for subjects meeting any of the following criteria:
    - "yes" or "no" response to the question "Did the subject complete 14 days of dosing?" on the Screening/Double Blind Subject Disposition eCRF
    - "yes" or "no" response to the question "Did the subject complete all VISITS in the Treatment Phase (Days 1 to 14 +/-1)?" on the Screening/Double Blind Subject Disposition eCRF
    - "yes" or "no" response to the question "Did the subject complete the Day 15 Visit?" on the Screening/Double Blind Subject Disposition eCRF

  - "yes, in-person visit", "yes, telephone visit", or "no" response to the question "Did the subject complete the Day 29 Visit"? on the Post-Treatment/Follow Up Disposition eCRF
  - "yes, in-person visit", "yes, telephone visit", or "no" response to the question "Did the subject complete the Day 60 Visit"? on the Post-Treatment/Follow Up Disposition eCRF.
- First planned database lock or after: Study drug end date/time.

This is an analysis period reference date.

- Last contact date:
  1. Earliest complete death date from the 6POSRS eCRF, if it exists.
  2. Otherwise, the latest complete date of the following: AE start or end; arterial blood gas collection; ECG; chest x-ray; hospital discharge; informed consent; CGRP plasma concentration specimen collection; IWRS randomization; laboratory test collection (clinical safety, experimental predictive marker, LFT, pregnancy, urinalysis); NEWS2 assessment; non-study medication start or end; physical exam; physical measurement; PK collection; PK concentration specimen collection; post-treatment/follow-up completion/discontinuation; procedure start or end; 6POSRS rating; SOFA assessment; study drug dose; subject journey; telephone contact; treatment phase completion/discontinuation; visit; vital sign.
  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.

  All dates are from eCRFs, except CGRP and PK concentration specimen collection dates are from an external source.
- Death date/time: (1) Earliest complete death date/time from the 6POSRS eCRF, if a complete date exists. If the time is missing, then it is set to 00:00. (2) Otherwise, the last contact date and time of 00:00. Derived only for subjects who died (see Section 6.4.1.1).
- Study discontinuation date: Last contact date derived only for subjects with nonmissing death date (see previous bullet) or nonmissing post-treatment/follow-up completion/discontinuation date. At the final planned database lock, the study discontinuation date is set to the last contact date.
- Initial ICU admission date: Earliest imputed AE start date of an intensive care AE (see Section 9.3).
- Imputed procedure start date: Defined analogously to the imputed AE start date as per Core SAP.
- Imputed procedure end date: Defined analogously to the imputed AE end date as per 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 date/times to analysis period reference date/times. Refer to the Core SAP for additional details.

Analysis periods are defined as follows:

- Pretreatment*: This period is used to derive baseline values and to assess pretreatment endpoints.
- On-treatment efficacy:
  - If the study drug last date is not missing: measurement date/time after the study drug start date/time through study drug last date + 1 day.
  - If the study drug last date is missing: measurement date/time after the study drug start date/time.

  This period is abbreviated as "ONTRT" in efficacy listings, and used to assess efficacy endpoints on treatment.
- Follow-up efficacy: measurement date after the study drug last date + 1 day. This period is abbreviated as "FU" in efficacy listings.
- On-treatment safety*: Note that AEs and procedures with imputed start date equal to the study drug start date are part of this period. Subject journey assessment dates equal to the study drug start date are also part of this period. This period is used to assess safety endpoints on treatment.
- Follow-up safety*: This period is used to assess safety endpoints during follow-up.
- On-study: measurement date/time after the study drug start date/time. Note that AEs and procedures with imputed start date equal to the study drug start date are part of this period. Subject journey assessment dates equal to the study drug start date are also part of this period. This period is used to assess efficacy and select safety endpoints. Note that this period is equal to the on-treatment and follow-up safety periods combined.

For analysis periods marked with "*", refer to the Core SAP for the definitions in Phase 2/3/4 multiple-dose studies with 1 treatment phase.

7.3 Analysis Visit Windows

Refer to Protocol Section 4.3 for the schedule of assessments.

Refer to the Core SAP for defining study days in Phase 2/3/4 multiple-dose studies with 1 treatment phase.

Table 6 presents analysis visit windows for efficacy and safety parameters.

Table 6 Analysis Visit Windows

Analysis Visit	Analysis-specified Interval	Target Study Day
Day 5	2 to 7	5
Day 10	8 to 13	10
Day 15	14 to 16	15
Day 22	20 to 24	22
Day 29	27 to 31	29
Day 60	45 to 75	60

Note that study day 1 may have both pretreatment and on-treatment measurements, depending on the measurement time.

7.3.1 Efficacy Measurements in Analysis Visit Windows

For select analyses using measurements over time, efficacy measurements are slotted into analysis visits using the following steps:

1. Measurements are slotted into the pretreatment and on-study analysis periods.
2. The following values are derived independently of steps 3 and 4:
   a. End of treatment (EOT), defined as the last nonmissing value in the on-treatment efficacy analysis period.
   b. End of study (EOS), defined as the last nonmissing value in the on-study analysis period
   c. Last on-study value before analysis visit Day *X* for each analysis visit.

   "Last" is determined by the measurement date/time and subject visit form ID.
3. Measurements are slotted into analysis visits in the on-study analysis period using analysis visit windows (Days 5, 10, 15, 22, 29, and 60). Note that some measurements may not be assigned an analysis visit.
4. If a subject has multiple values in an on-study analysis visit window, then the following algorithm is used:
   a. Days 5, 10, {15 with time on study drug ≤ 14 days}, 22, 29, and 60: The nonmissing value closest to the target day for the analysis visit is used; in the case of a tie, the last value collected is used, as determined by the measurement date/time and subject visit form ID.
   b. Day 15 with time on study drug ≥ 15 days: Last nonmissing value on study day 16, if available. Otherwise, the selection process is like step 4a.

Time on study drug is defined in Section 6.2.6.1. See Sections 7.1, and 7.2 for definitions of derived dates and analysis periods, respectively.

7.3.2 Safety Measurements in Analysis Visit Windows

For select analyses using measurements over time, safety measurements are slotted into analysis visits using the following steps:

1. Measurements are slotted into the pretreatment and on-study analysis periods.
2. The following values are derived independently of steps 3 and 4:
   a. End of treatment (EOT), defined as the last nonmissing value in the on-treatment safety analysis period.
   b. End of follow-up (EOFU), defined as the last nonmissing value in the follow-up safety analysis period
   c. End of study (EOS), defined as the last nonmissing value in the on-study analysis period.

   "Last" is determined by the measurement date/time and subject visit form ID.
3. Measurements are slotted into analysis visits in the on-study analysis period using analysis visit windows. The phrase "Day *X*" denotes the Day *X* analysis visit window, where *X* = 5, 10, 15, 22, 29, and 60. Note that some measurements may not be assigned an analysis visit.
4. If a subject has multiple values in an analysis visit window, then the nonmissing value closest to the target day for the analysis visit is used; in the case of a tie, the last value collected is used, as determined by the measurement date/time and subject visit form ID.

See Sections 7.1, and 7.2 for definitions of derived dates and analysis periods, respectively.

8 CONTENT OF REPORTS

The final CSR was planned after the last planned analysis (after the last subject reached Day 60). The CSR is not produced due to premature study termination.

The abbreviated CSR is produced after database lock in 4Q2022. All analyses described in this SAP are included.

9 APPENDICES

9.1 Procedures Used for Efficacy Endpoints

Procedures are from the Concomitant Procedures eCRF.

All days from the imputed procedure start date to the imputed procedure end date inclusive are considered to be procedure days. See Section 7.1 for imputed procedure start and end dates.

A procedure day is considered to be on study if it is on or after the study drug start date.

A procedure is considered to be on the same day as a measurement (e.g., 6POSRS rating) if the study day of the measurement date is a procedure day.

A procedure is considered to be at Day *X* if there is ≥ 1 procedure day in the Day *X* analysis visit window, i.e., between the lower and upper bounds of the analysis visit window inclusive.

A procedure is considered to be before Day *X* if there is ≥ 1 procedure day before the Day *X* analysis visit window.

A procedure is considered to be through Day *X* if there is ≥ 1 procedure day in or before the Day *X* analysis visit window.

9.1.1 Invasive Mechanical Ventilation Use

Invasive mechanical ventilation use is defined as any of the following procedures: use of ventilator machine with mask or mouthpiece; use of ventilator machine with endotracheal tube; intubation for mechanical ventilation; use of extracorporeal membrane oxygenation device.

9.1.2 Ventilation Use

Ventilation use is defined as (1) invasive mechanical ventilation use as per Section 9.1.1, or (2) any of the following non-invasive ventilation procedures: use of partial rebreather; use of oxygen mask; use of non-rebreather; use of venturi mask; use of bag valve mask; use of non-invasive ventilation (NIV) system; use of tracheostomy mask; use of continuous positive airway pressure (CPAP) mask.

9.1.3 Low-Flow or High-flow Nasal Cannula Use

Low-flow or high-flow nasal cannula use is defined as procedures of low-flow nasal cannulation or high-flow nasal cannulation.

9.1.4 Ventilation or High-flow Nasal Cannulation Use

Ventilation or high-flow nasal cannulation use is defined as (1) ventilation as per Section 9.1.2, or (2) a procedure of high-flow nasal cannulation.

9.1.5 Supplemental Oxygen Use

Supplemental oxygen use is defined as (1) ventilation use as per Section 9.1.2, or (2) low-flow or high-flow nasal cannula use as per Section 9.1.3.

9.2 Procedures in Analysis Periods

Procedures are slotted into analysis periods according to both imputed procedure start and imputed procedure end dates (see Section 7.1). A procedure may be slotted into multiple analysis periods.

Pretreatment procedures are defined as those with imputed start or imputed end date < study drug start date.

On-treatment safety procedures are defined as those meeting any of the following criteria:

- Study drug start date ≤ imputed start or imputed end date ≤ study drug last date + 7 days
- Study drug start date ≤ imputed start or imputed end date and study drug last date is missing
- Imputed start date ≤ study drug start date ≤ study drug last date + 7 days ≤ imputed end date
- Imputed start date ≤ study drug start date ≤ imputed end date and study drug last date is missing.

Follow-up safety procedures are defined as those with study drug last date + 7 days < imputed start or imputed end date.

On-study procedures are defined as those with imputed start or imputed end date ≥ study drug start date. Thus, on-treatment and follow-up procedures are subsets of on-study procedures.

9.3 Intensive Care AEs

Intensive care AEs are those with a PT of "intensive care".

All days between an imputed AE start date to an imputed AE end date inclusive are considered to be intensive care AE days. Imputed AE start and end dates are defined in the Core SAP.

An intensive care AE is considered to be at Day *X* if there is ≥ 1 intensive care AE day in the Day *X* analysis visit window, i.e., between the lower and upper bounds of the analysis visit window inclusive.

An intensive care AE is considered to be through Day *X* if there is ≥ 1 intensive care AE day before or in the Day *X* analysis visit window.

10 REFERENCES

Not applicable.