DRUG:	Zavegepant
STUDY NUMBER(S):	BHV3500-203
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
IND NUMBER:	CCI
EudraCT NUMBER: (if applicable)	NA
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	13 April 2020
VERSION NUMBER:	V 7.0
VERSION DATE:	11 May 2022

SUMMARY OF CHANGES

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	13 April 2020
Version 2.0	• Incorporation of Administrative Letter #1: clarification of Visit Day vs. Calendar Day and addition of windows to Day 14, Day 15, and Day 16. • CCI [redacted] • Clarification around dosing every 8 hours to allow for a window of +/- 2 hours • Clarification of Inclusion Criteria #6 to specify non-invasive supplemental oxygen • Clarification of Exclusion Criteria # 1to specify invasive mechanical ventilation. • Change to exclusion #8 to allow for 48 hours of supplemental oxygen prior to randomization • Clarification to exclusion criteria #9 to define severe COPD as exclusionary • Change to Exclusion Criteria #13 to allow for subjects with ALTs and ASTs up to 5x ULN to be allowed • Clarification of Secondary Objectives #2, 4, and 5 to specify invasive mechanical ventilation • Clarification of Secondary Objective #8 to specify SpO2/FiO2 ratio • Reordering of Secondary Objectives and Secondary Endpoints • Clarification throughout the protocol that creatinine clearance is assessed via measurement of eGFR • Removal of MDRD as the required calculation for eGFR • Update to Study Schematic Changes throughout the protocol to allow Clinical Safety labs, LFTs, urinalysis, NEWS2 assessments, Vitals, PE, SpO2, FiO2, ECG, and chest x-ray collected within 48 hours of signing Informed Consent to be used as Screening assessments. • Clarification throughout the protocol that clinically important clinical labs, urinalysis, LFTs, ECGs, and chest X-rays that are collected as per SOC on non-	06 May 2020

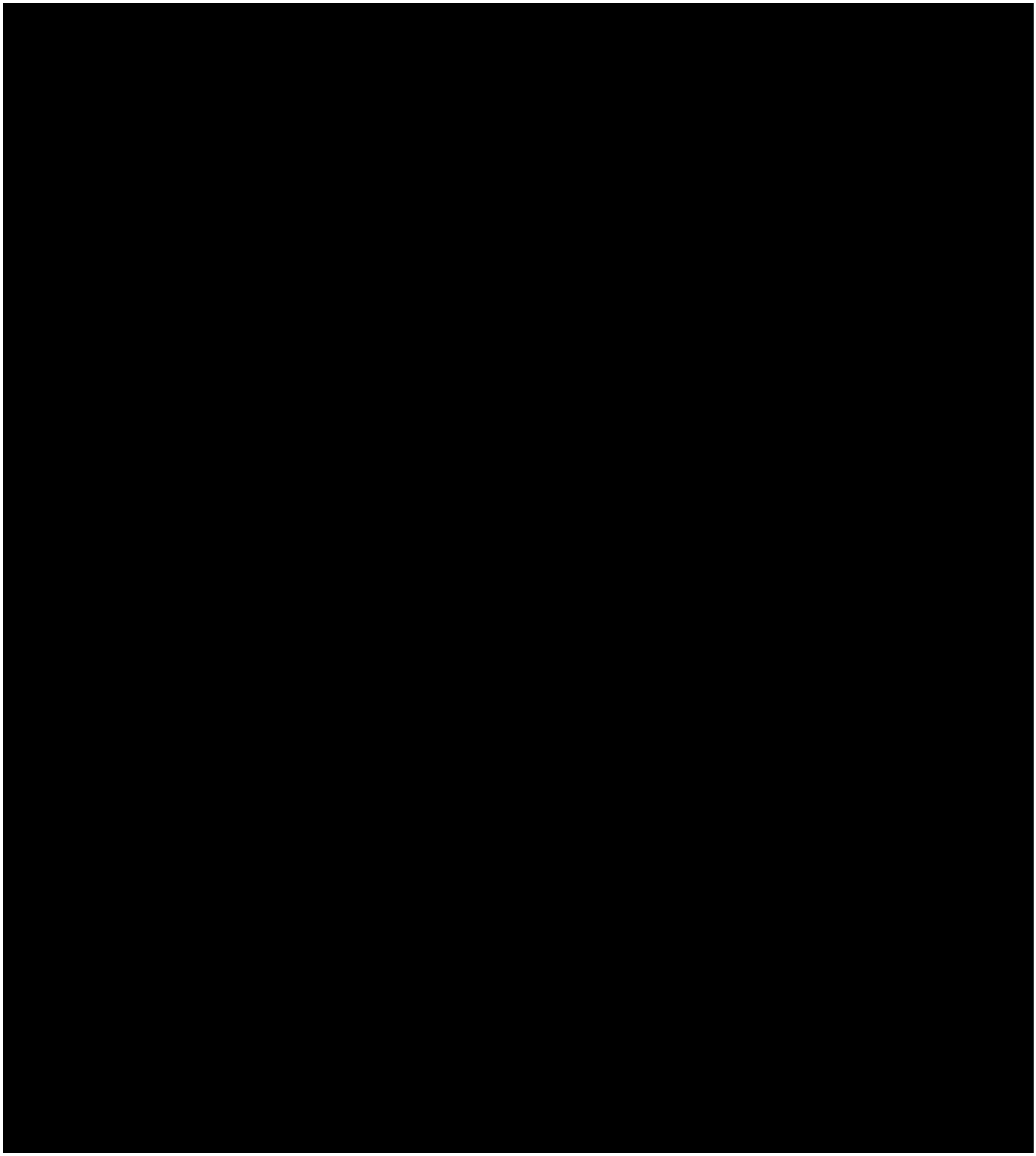
	protocol specified days should be collected in the eCRF from Days 1 through 29 • Clarification throughout the protocol that SOFA is collected upon admission to the ICU and collected again, only if subject is still in ICU at Day 29 • Clarifications to Schedule of Assessments • Clarification about collection of serum sample for SARS-CoV2 antibody analysis and sample for CGRP evaluation • Clarification of Day 60 Safety Follow-up visit • Clarification to early discontinuation from investigational product • Change to Early Discontinuation from the Study parameters to correct typo. • Clarifications to Dose and Administration to specify completing treatment as completing 42 doses of study drug • Change to Definition of Serious Adverse Event to include admission to the ICU as an SAE • Update to Collection and Reporting of Serious Adverse Events to provide email information for PVG vendor • The analysis of the primary endpoint was changed to use a Mixed Model for Repeated Measures. • Clarification made to Missing Data for the Mixed Model for Repeated Measures • Various typos have been corrected	
Version 3.0	• Correction of minor typos throughout the document • Specification throughout the protocol that subjects whose eGFR declines to < 15 mL/min will be discontinued from study drug • Further clarification throughout the protocol that EOT is when the patient takes the last dose of study drug which may not necessarily be Day 15 and that if an EOT visit is performed prior to subject completing treatment, then Day 15 is a telephone visit • Change to Exclusion Criteria # 2 to exclude patients with eGFR < 30 mL/min from < 60 mL/min • The wording for objectives that involved "numbers of subjects" or "percentages of subjects" was harmonized to "proportion of subjects" • Clarification of wording for Secondary Objective # 24	19 June 2020

	• CCI [redacted] • CCI [redacted] • CCI [redacted] • Minor changes to the study schematic • Inclusion of Section 1.3.3 to provide rationale to include patients with eGFR 2. 30 mL/min into the trial. Subjects whose eGFR drops to <15 mL/min while on study will be discontinued from study drug. • The wording of the primary endpoint was clarified to indicate the treatment groups will be compared based on their average difference on the 6 point severity scale. • The wording for endpoints that involved "numbers of subjects" or "percentages of subjects" was harmonized to "proportion of subjects" • Clarification of wording for Secondary Endpoint # 24 • Clarification that Visit Days 22 and 29 have a window of +/- 2 days • Clarification of the Schedule of Assessments to specify AE and SAE collection periods, CCI [redacted] and to specify urinalysis and safety labs that need to be collected in the table • Additional clarifications to descriptions in the Schedule of Assessments for chest x-ray collection, concomitant medication collection, and Telephone visits • Clarification of Sections 4.3.6.1 and 4.3.6.2 surrounding the timeframe for capturing of AEs and SAEs • Clarification to Section 4.3.7 about collection of SAEs • Update to Section 6.1 concerning labels for CGRP samples and clarification about the local laboratory collection • Clarification to Section 6.3.5 to specify that clinically significant laboratory abnormalities need to be collected out to Day 29 • Clarification to Section 6.3.5.1 to match order of lab collection data in eCRF • CCI [redacted] • Clarification in Section 6.3.5.3 to indicate Syneos Laboratory Manual for PK sampling and to provide further clarification around the collection of PK	

	samples. • Clarification to Section 6.3.5.4 about the serum sample for SARS-CoV2 antibody testing • Change to section 6.6 to adjust requirement to discontinue subjects from study drug if eGFR drops to < 15 ml/min • Clarification to Section 7.2 to specify that when possible, drug should be dispensed if subject is transferred to another acute care facility • Further clarification to Section 8.3.1 (Definition of Serious Adverse Event) to define situations which may be considered as SAEs. • Clarification for collecting SAEs made to Section 8.3.2 • Moved SAE sections of Overdose, Pregnancy and DILI to from Section 8.4 to Section 8.3 for flow – no language changes made to those sections • Clarification to Section 8.4.1 regarding the time period for collection of AEs • Clarification to Section 8.4.2 regarding the time period for collecting lab abnormality AEs	
• Version 4.0	• Incorporation of Administrative Letter #3: Change of Generic Name for BHV-3500 from “Vazegepant” to “Zavegepant”.The generic name of BHV-3500 was revised from “vazegepant” to “zavegepant” throughout the protocol. Since August 2019, "vazegepant" has been used for BHV-3500 after this non-proprietary name was approved for use in the U.S. by the United States Adopted Names (USAN) Council. In May 2020, the organization responsible for establishing non-proprietary names for international use (the World Health Organization (WHO) International Nonproprietary Names (INN) Expert Committee) revised the name to "zavegepant". This change has been subsequently accepted by the USAN Council for use in the U.S. and is pending formal adoption by the INN for international use. • The collection of concomitant procedures, which are captured from first dose of study drug through Day 29 (except for the start of supplemental oxygen within 48 hours of randomization) has been added throughout the protocol.	12 August 2020

	• Clarifications made to Secondary Objectives to define the population for analysis. • The Study Schematic has been updated to reflect concomitant procedures collection. • The Schedule of Assessments has been updated to include collection of concomitant procedures, identification that admission and discharge from the ICU should be captured on the AE eCRF, and clarification of the collection of the SOFA assessment. • eCRF sources were clearly defined for efficacy measures, thus, endpoint definitions were modified to all relevant sources • Clarification to collection of ECG data beyond screening if clinically significant and to collect all chest X-ray data if done as SOC beyond Day 15. • CCI [redacted] • Clarification to Section 8 to indicate that for this study, admission and discharge to the ICU needs to be captured on the Adverse Event eCRF. • Clarification that laboratory test data related to an SAE should be collected out to Day 60. • Clarifications made to the statistical methods Section 9.3.	
Version 5.0 (note Version 5.0 Protocol was completed and approved on 09 Nov 2020 but not submitted because an error in one of the figures was discovered.It is superseded by version 6.0)	• Removal of the requirement for the specific Abbot IgG antibody test. • Specification that antibody test needs to be done no earlier than Day 15 and before Day 60. • Updates concerning antibody testing in the Study Schematic and Schedule of Assessments, • Punctuation corrections throughout the protocol. • Clarification of the wording in Section 9.3. Statistical Methods section.	09 November 2020
Version 6.0	• Corrected Study Schematic – version for submissions	10 Nov 2020
Version 7.0	• The headers were changed to reflect the new version number. • The cover page was updated to reflect the new version number and date. • Typos corrected in Exclusion Criteria #11 in the Synopsis and Section 5.3	11 May 2022

	• CCI [redacted] • CCI [redacted] • Section 3.2 was updated to describe the CRFs to be used to analyze secondary endpoints • CCI [redacted] • Section 9.3.3 was updated to reflect the changes of secondary endpoints to exploratory endpoints.	



STUDY SUMMARY (SYNOPSIS)

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
Rationale:	Zavegepant (BHV-3500) is a potent calcitonin gene-related peptide (CGRP) receptor antagonist. Acute lung injury induces upregulation of transient receptor potential (TRP) channels which activates CGRP leading to both acute lung injury (pulmonary edema with acute phase cytokine/mediator release, with immunologic milieu shift toward Type 17 helper (Th17) cytokines) followed by chronic lung injury with hyaline membrane formation, fibrosis and reduced diffusion capacity. Acute respiratory distress syndrome (ARDS), which is a common pathway resulting from diverse types of lung injury is part of this pathogenic process. Because Coronavirus Disease 2019 (COVID-19), which is caused by infection with serious acute respiratory syndrome coronavirus-2 (SARS-CoV-2), leads to an acute insult of pulmonary epithelia, we postulate that a CGRP receptor antagonist may potentially blunt the severe inflammatory response at the alveolar level, delaying or reversing the path towards oxygen desaturation, ARDS, requirement for supplemental oxygenation, artificial ventilation or death. The data from this study will allow characterization of the relative safety and efficacy of IN zavegepant versus placebo in the treatment of COVID-19 infection leading to hospitalization.
Target Population:	The study will recruit male and female subjects 18 years of age and older with polymerase chain reaction (PCR)-documented COVID-19 infection that necessitates supplemental oxygen at the time of hospitalization.
Number of Subjects:	Approximately 180 subjects will be screened to randomize approximately 120 subjects. The subjects will be randomized in a 2:1 ratio to the zavegepant (80 subjects) or placebo (40 subjects) treatment groups. Randomization will be done through an IWRS, that will be accessed by the unblinded research pharmacists or their designees. The randomization scheme will be stratified by age (<60; 2. 60).
Objectives:	**Primary**: To evaluate the safety and efficacy of zavegepant (BHV-3500) compared with placebo in subjects hospitalized with COVID-19 infection requiring supplemental oxygen.

Study Hypothesis:	Zavegepant reduces and slows the progression of the disease and improves overall outcome of COVID-19 infection.
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 drug will be zavegepant 10 mg or matching placebo, given as an intranasal (IN) dose every 8 hours (+/- 2 hours) for approximately 14 days (total of 42 doses). The study will randomize approximately 120 subjects in a 2:1 ratio across the two treatment groups (zavegepant or matching placebo). The randomization will be stratified by age (less than 60 years vs 60 years and older). After signing informed consent and meeting eligibility criteria, the subject may be immediately randomized and dosed with the double-blind study medication (10 mg or matching placebo) and continue dosing every 8 hours (Q8h) for approximately 14 days (total of 42 doses). For the purposes of this protocol, the start of Visit Day 1 will start when the 1st dose of study drug is administered until 24 hours later. Therefore, depending on the time the 1st dose of study drug is administered, a visit day may spread over 2 calendar days. The last dose of study drug could be administered on Visit Day 14 but could actually occur on calendar day 15 of the study. The EOT assessments should be completed after the last dose of study drug and before discharge from the hospital and the subjects should remain in the hospital for a full 24 hours after their last dose of drug if they are to be released. If subjects complete all 42 doses of study drug, the Day 15 in-person visit is the same as the EOT visit. Randomization will be done through an IWRS, that will be accessed by the unblinded research pharmacists or their designees. so that subjects can be dosed as soon as possible following consent and assessment of eligibility criteria. After completion of treatment, subjects will be followed out to Day 60 during the post treatment phase.
Inclusion Criteria	1. Subjects must provide informed consent in accordance with requirements of the study center's institutional review board (IRB) or ethics committee, prior to the initiation of any protocol-required procedures 2. Subjects must agree to provide all requested demographic information (i.e. gender, race) 3. Subjects must be able to read and understand English or Spanish 4. Subjects must be over the age of 18 years

	5. Subjects must have laboratory-confirmed SARS-CoV-2 infection as determined by PCR-based commercial or public health assay 6. Subjects must have symptoms that require hospitalization with supplemental oxygen and or non-invasive ventilation as determined by the admitting physician. The maximum nasal cannula O_2 concentration should be determined by the treating clinician and the limitations of the specific equipment 7. Subjects must be willing and able to comply with study-related procedures/assessments
Exclusion Criteria	1. Subjects in immediate need of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) 2. Subjects with an estimated glomerular filtration rate (eGFR) of < 30 mL/min, at the Screening Visit 3. Prisoners or subjects who are involuntarily incarcerated 4. Subjects who are participating in any other investigational clinical trial while participating in this clinical trial 5. Subjects under the age of 18 years 6. Subjects who are pregnant (all potential female enrollees to have negative pregnancy test prior to investigational product [IP] administration) 7. Subjects with multi-organ failure 8. Subjects who have received more than 48 hours of supplemental oxygen prior to randomization 9. Subjects with prior significant pulmonary disease (e.g., severe chronic obstructive pulmonary disease [COPD]/ interstitial lung disease [ILD]/congestive heart failure [CHF]/idiopathic pulmonary fibrosis [IPF]) are excluded 10. Subjects receiving investigational therapies as part of a formal clinical trial for the treatment of COVID-19. During the course of this study, investigational therapies that may become “standard of care” to treat COVID-19, but are not part of a clinical trial, are allowed 11. Subjects who are on long-acting CGRP monoclonal antibodies including Aimovig® (erenumab), Emgality® (galcanezumab), Ajovy®

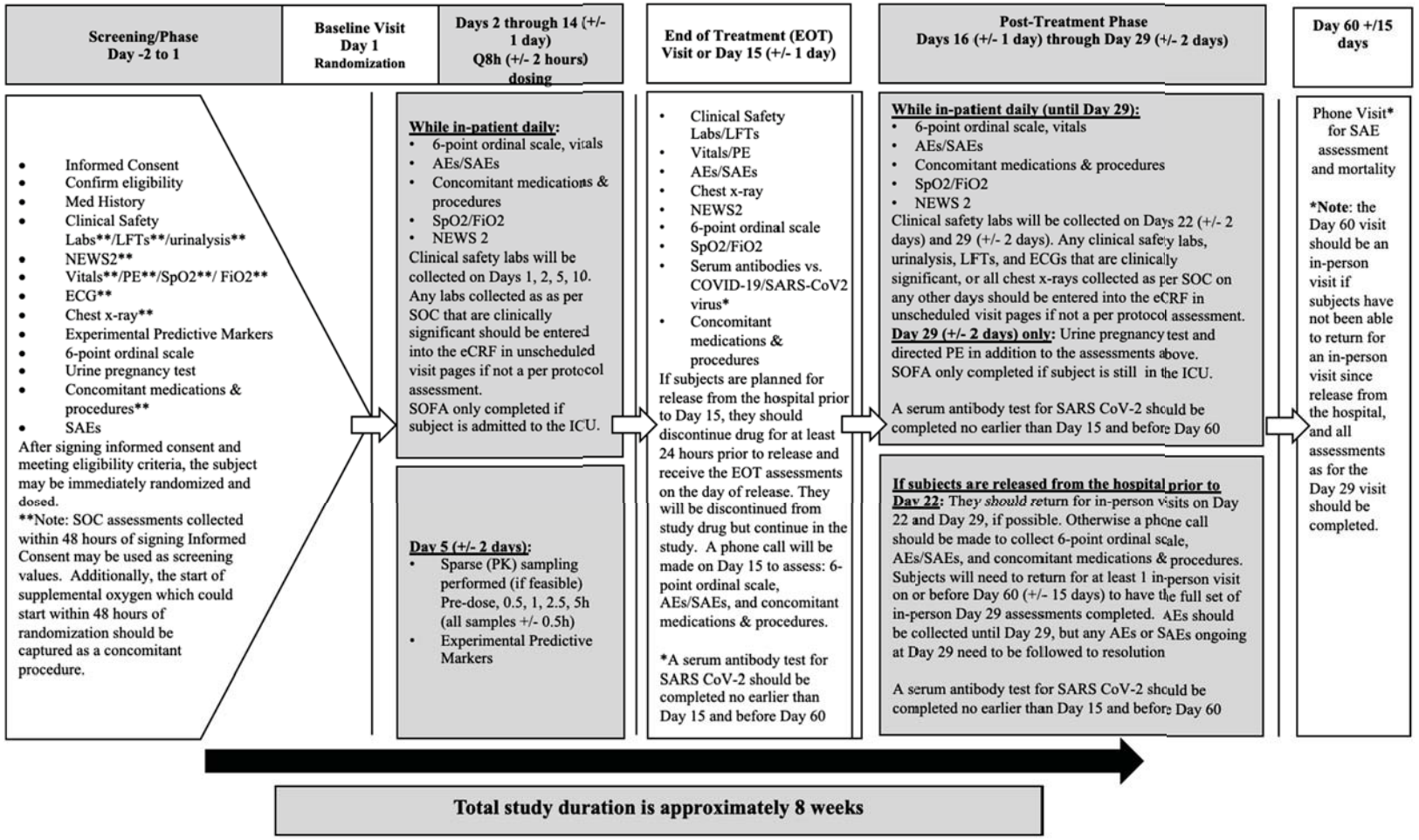
	(fremanezumab), and Vyepti® (eptinezumab). Additionally, the investigational oral CGRP receptor antagonist, atogepant, that is taken daily is excluded. Oral CGRP receptor antagonists, Nurtec® ODT (rimegepant) and Ubrelvy™ (ubrogepant) that are typically used PRN infrequently will not be excluded as long the subject was not taking them on a daily basis and does not take them during the current stud 12. Subjects who are unlikely to survive for more than 48 hours from the Screening Visit 13. Subjects with any of the following abnormal laboratory values at screening: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5x upper limit of normal (ULN) or bilirubin greater than 2x upper limit of normal 14. Subjects with known active tuberculosis (TB), history of incompletely treated TB, suspected or known extrapulmonary TB 15. Subjects with suspected or known systemic bacterial or fungal infections. However, empiric antibiotics are permitted 16. Subjects who have participated in any clinical research study evaluating an IP or therapy within 3 months and less than 5 half-lives of IP prior to the screening visit 17. Subjects with any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study
Primary Objective:	To compare the efficacy of zavegepant (BHV-3500) to placebo, in subjects hospitalized with COVID-19 infection requiring supplemental oxygen, using a six-point rating scale at Day 15
Secondary Objectives	**<u>Key Secondary Objectives</u>** 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 nasal cannula through Day 29 3. To compare zavegepant to placebo on the proportion of subjects admitted into an intensive care unit (ICU) through Day 29 **<u>Other Secondary Objectives</u>**

	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 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 function, defined as at least 50% reduction in eGFR from baseline
CCI	[redacted]


CCI

CCI [redacted]	[redacted]

STUDY SCHEMATIC



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LIST OF ABBREVIATIONS

ABG	Arterial Blood Gas
AE	Adverse Event
ALI	Acute Lung Injury
ALT	Alanine Aminotransferase
AM	Morning
ARDS	Acute respiratory distress syndrome
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BHV-3500	Zavegepant
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca2+	Calcium ion
CGRP	Calcitonin Gene-Related Peptide
CHG	Congestive heart failure
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ER	Emergency Room
eTMF	Electronic Trial Master File

FiO2	Fraction of Inspired Oxygen
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	Hour(s)
HbA1c	Hemoglobin A1c
HR	Heart Rate
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IL	Interleukin
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IN	Intranasal
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
i.v.	Intravenous
kg	Kilogram
L	Liters
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome-Related Coronavirus
mg	Milligram
min	Minute
MTD	Maximum Tolerated Dose
NEWS2	National Early Warning Score 2
PCR	Polymerase Chain Reaction

PE	Physical Exam
PID	Patient Identification
PK	Pharmacokinetic
PM	Evening
p.o.	By Mouth, Orally
PVG	Pharmacovigilance
Q8h	Administered Every 8 Hours
QD	Once Daily
RBC	Red Blood Cell
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SpO2	Peripheral Capillary Oxygen Saturation Measured by Pulse Oximeter
SpO2/FiO2	Ratio of Pulse Oximeter-Measured Oxygen Saturation to Fraction of Inspired Oxygen
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
Th17	Type 17 Helper
TNF	Tumor Necrosis Factor
TRP	Transient Receptor Potential
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Therapeutic Area Background

Coronavirus Disease 2019 (COVID-19) infection presents with respiratory symptoms and fever in the majority of patients.[1,2] Among patients requiring hospitalization, the majority develop pulmonary infiltrates. The virus that causes COVID-19, SARS-CoV-2, as with SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV), can induce an excessive and aberrant non-effective host immune responses that is associated with severe lung pathology, leading to death.[2-4] Similar to patients with SARS-CoV and MERS-CoV, some patients with SARS-CoV-2 develop ARDS with characteristic pulmonary ground glass changes on imaging. In most patients who develop critical disease, SARS-CoV-2 infection is associated with a cytokine storm, with high levels of IL-6 and other proinflammatory cytokines being associated with poor outcomes.[5,6] Similar cytokine storm pathology and outcomes has been described for SARS-CoV and MERS-CoV.[7] A recent single arm study in 20 COVID-19 patients in China suggests that targeting IL6 with anti-IL-6 antibody may have clinical benefit,[8] and several studies are initiating to study anti-IL-6 treatment in a controlled manner.

In patients who develop acute lung injury (ALI)/ARDS due to coronavirus infection who go on to survive intensive care, the excessive immune response leads to long-term lung damage and fibrosis, causing functional disability and reduced quality of life.[9,10]

An important downstream effect of CGRP release is upregulation and release of IL-6 from a variety of cell types in different diseases.[11-18] CGRP also drives T-cell polarization towards a Th17 response.[17,19-21] Consequently, the treatment of COVID-19 by an agent that blocks the CGRP receptor my provide therapeutic benefit in this disease state by inhibiting the downstream IL-6 and/or Th17 sequelae, and forms the basis of this proposal.

1.1.1 CGRP Background

Calcitonin gene-related peptide, or CGRP, is a pleotropic neuropeptide that is primarily released in response to activation of TRP ion channels.[22] Originally, TRP channel physiology focused on its fundamental meaning in sensory neuronal function. However, it is now known that activation of diverse TRP ion channels in multiple cell types results in neuropeptide release and consecutive neurogenic inflammation, with TRPV1[22] TRPV4[23] and TRPA1[2,24] known to be responsible for CGRP release.

The TRP channel is a non-selective cation channel predominately permeable for calcium ion (Ca2+),[25] and is directly activated by chemical, thermal (e.g. fever), and mechanical stimuli, including infectious disease stimuli.[20,26-29] TRP channels are ubiquitously expressed in dinerent tissues and cell types and are a key player in the regulation of intracellular calcium. Viruses require Ca2+ for replication and respiratory viruses, including coronavirus, have been reported to increase the expression of these channels in sensory neurons and human bronchial epithelium cells[25,30,31] to facilitate replication.

As a result of its connection to TRP channel activation, CGRP is released and is pleotropic effects involved in a variety of acute lung injuries diseases.[32,33] CGRP receptor antagonists have been shown to reduce proximal airway necrosis by 40% and terminal bronchiole necrosis by 50% in chemical acute lung injury.[32] Blockade of TRPV4, or downstream CGRP, could be an important therapeutic approach in managing edema and acute lung injury in inflammatory lung diseases.[34-36]

An important downstream effect of CGRP release is upregulation and release of IL-6 from a variety of cell types in different diseases.[11-18]

CGRP regulates T-cell function via T-cells' interaction with dendritic cells (DCs) and macrophages, both of which express the CGRP receptor.[37,38] In various diseases in which CGRP signaling becomes dysfunctional, including those induced by aberrant TRP activation, CGRP drives T-cell polarization towards a Th17 response.[17,19-21] In fact, deletion of a crucial subunit of the CGRP receptor has been shown to ameliorate Th17 autoimmunity.[21]

1.1.2 Product Development Background

Details of the clinical and preclinical studies are provided in the most current version of the Investigator's Brochure. [39]A summary of the relevant data is presented below.

1.1.2.1 Non-clinical Pharmacology, Pharmacokinetics, Pharmacodynamics and Toxicology

A series of in vitro and in vivo pharmacokinetic (PK) and metabolism studies were conducted with zavegepant in rats, dogs, rabbits, mice and monkeys. Safety studies in were also performed in rat and monkey to determine tolerability, potential for local irritation, and to assess systemic toxicity. The details of these studies can be found in the Zavegepant (BHV-3500) Investigator Brochure (IB).[39]

1.1.2.2 Clinical Experience

CCI [redacted]

[redacted]

CCI

[redacted]

1.1.2.3 Other Clinical/Non-Clinical Studies

A series of in vitro studies have been performed to investigate CYP-mediated drug interactions. Zavegepant has been examined for effects in a transporter study.[40] The details of these studies can be found in the Zavegepant (BHV-3500) IB.[39]

1.1.2.4 Clinical Adverse Event Profile

1.1.2.4.1 Phase 2/3 Dose Ranging Study (BHV3500-201)

BHV3500-201 is a concluded, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study conducted to evaluate the safety and efficacy of zavegepant (5 mg, 10 mg, or 20 mg) of a single dose of zavegepant IN versus placebo in the acute treatment of migraine.

No deaths were reported, and no treatment-related SAEs were reported. SAEs were reported on-treatment in two subjects including post-traumatic thrombosis reported in one subject in the zavegepant 10 mg group, and vestibular migraine reported in one subject in the placebo group. Both events were moderate in intensity and judged by the investigator as not related to study drug.

The overall incidence of AEs was 26.2% (311 of 1,185 subjects) in the zavegepant groups and 15.4% (62 of 403 subjects) in the placebo group. The incidence of AEs in the zavegepant groups were as follows: 22.7% (88 of 388 subjects) in the 5 mg group, 24.6% (97 of 394 subjects) in the 10 mg group, and 31.3% (126 of 403 subjects) in the 20 mg group. The majority of AEs were mild in intensity. The table below presents the most frequently reported (2. 1% in any zavegepant group) AEs in the zavegepant groups.

BHV3500-201 Most Frequently (≥1%) Reported AEs					
No. Treated	**(N=388)**	**(N=394)**	**(N=403)**	**(N=1185)**	**(N=403)**
Adverse Event	**5 mg**	**10 mg**	**20 mg**	**Overall zavegepant**	**Placebo**
Dysgeusia	13.9%	13.5%	16.1%	14.5%	3.5%
Nausea	2.6%	4.1%	2.7%	3.1%	0.5%
Nasal Discomfort	1.3%	1.3%	5.2%	2.6%	0.2%
Throat Irritation	1.0%	1.0%	2.2%	1.4%	0.0%
Vomiting	0.3%	1.8%	1.7%	1.3%	0.2%
UTI	0.8%	1.0%	2.0%	1.3%	1.2%

Nasal inspection conducted at screening, baseline and end of treatment showed no clinical evidence of nasal mucosal injury. No subject had AST or ALT > 3x ULN or bilirubin > 2x ULN in any treatment group.

The first-generation small molecule CGRP antagonists (e.g. telcagepant and MK-3207), have shown effects on elevated transaminases and hypertension. The liver effects of these compounds were thought to be related to the chemical structures and off-target effects of antagonizing CGRP receptors[41].

Additional information with next generation monoclonal antibodies targeting CGRP receptors (e.g. Aiomivig) and other small molecules (e.g. Ubrelvy and Nurtec ODT) have not shown similar liver safety issues. Zavegepant is a third-generation CGRP receptor antagonist that is structurally unrelated to the first-generation small molecule CGRP receptor antagonists. Liver effects have not been observed with zavegepant; however, liver safety and blood pressure will be monitored in this study.

1.2 Study Rationale

There is an urgent need to assess both antiviral mechanisms but also host innate mechanisms to combat the COVID-19 pandemic.[5,42] Given the urgent need to test novel mechanisms to combat COVID-19 infection, the pleotropic function of CGRP as a key mediator of the neuro-immune system warrants assessment of the potential for CGRP-antagonism in mitigating the hyper-immune disease characteristic of serious COVID-19 infection. This study will assess the hypothesis that antagonizing CGRP receptors in a variety of neural and immune cells within the respiratory tract in the setting of COVID-19 infection will decrease both acute inflammation and edema formation and reduce the subsequent risk of developing interstitial lung diseases (ALI/ARDS) resulting from a hyper-inflammation immune response.

1.3 Dosing Rationale

1.3.1 Zavegepant Properties

Zavegepant has multiple properties which render it an ideal molecule for near-term treatment of COVID-19, including (as detailed below), high CGRP receptor affinity, clinical proof-of-concept in migraine for 10 mg intranasal dose, ~6 hour half-life, hospital- and patient-friendly Aptar device usable in ventilation patients, clinical safety with up to 14 days of dosing, Good Manufacturing Practice (GMP) clinical supplies available now, and high aqueous solubility with potential for alternate (i.v., p.o.) formulations:

- Ultra-high affinity for the human CGRP receptor (K_i = 0.023 nM) that can displace CGRP from the receptor and blocks the effects of ongoing CGRP release

- Clinical efficacy already demonstrated with 10 mg intranasal dose in the acute treatment of migraine; showing ability block a human disease state associated with high CGRP release

- Short half-life of ~6 hours allows it to be withdrawn and quickly cleared if needed, while also providing durable CGRP receptor occupancy with 8 hour dosing (see Section 1.3.2 Rationale for Dose Selection)

- Intranasal route of delivery that's usable even in patients on ventilation or nasal cannula respiratory support

- The device is familiar, simple to use, disposable, Aptar nasal spray single-shot technology that's already used in hospital settings to treat opioid overdose (Narcan™)

- Safety and tolerability of nasal zavegepant have already been demonstrated in humans with multiple doses up to 40 mg daily for 8 days and 20 mg daily for 14 days. The selected zavegepant dose of 10 mg IN every 8 hours is expected to produce a geometric mean Cmax of 13 ng/mL and AUC over 24 h of 92.7 ng-h/mL (extrapolating from 14 days of dosing up to 10 mg IN once daily (QD) in Study 3500-102). The highest geometric mean Cmax and AUC over 24 h obtained in Study 3500-102 after dosing 20-40 mg IN for up to 14 days were 24.6-40.9 ng/mL and 87.9 to 94.2 ng-h/mL, respectively. Thus, zavegepant 10 mg every 8 hours IN is expected to produce a Cmax at least 2-3 fold lower and an AUC over 24 hours similar to that produced by the highest doses given to humans for up to14 days.

- GMP clinical supplies are currently on-hand and available (diverting units from our planned second Phase 3 migraine study)

- High aqueous solubility (> 300 mg/mL) provides for multiple routes of administration; upon successful proof-of-concept can be readily reformulated as intravenous, subcutaneous or oral agent to provide dosing options for inside and outside the hospital setting

1.3.2 Rationale for Dose Selection

Zavegepant 10 mg IN delivered every 8 hours provides durable coverage for CGRP receptor occupancy to test the effect on COVID-19:

- Human PK data were used to conduct steady state simulations
- CCI
- CCI
- The clinical safety and tolerability of nasal zavegepant have already been demonstrated in humans with multiple doses up to 40 mg daily for 8 days and 20 mg daily for 14 days. The selected zavegepant dose of 10 mg IN every 8 hours is expected to produce a Cmax at least 2 to 3-fold lower than, and an AUC over 24 hours similar to, that produced by the highest doses given to humans over 14 days (see details in Section 1.3.1).

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1.3.3 Rationale for Including Patients with Renal Impairment

Zavegepant is metabolically stable and primarily excreted unchanged as parent compound. A recently completed rat ADME study where [14C]-BHV-3500 was intravenously administered to rats[44] showed that the majority (~85% dose) of radioactivity was recovered during the first 48 hours with feces (64%) as the major route of elimination and a more minor contribution via renal (24%) elimination.

Consistent with these results, in the human zavegepant MAD and SAD studies,[39] there was no evidence of renal injury.

Subjects with estimated creatinine clearance 2. 30 mL/min will be allowed into the study. Subjects who develop eGFR <15 mL/min while on study should be discontinued from the study drug.

1.4 Research Hypothesis

Zavegepant reduces and slows the progression of the disease and improves overall outcome of COVID-19 infection.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

2.2.1 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 nasal cannula through Day 29.
3. To compare zavegepant to placebo on the proportion of subjects admitted into an intensive care unit (ICU) through Day 29.

2.2.2 Other Secondary Objectives

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.
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 function, defined as at least 50% reduction in eGFR from baseline.

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3 STUDY ENDPOINTS

3.1 Primary Endpoint

Efficacy will be measured by the difference between treatment groups in the mean 6-point severity rating at Day 15. The severity ratings are:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen
6. Not hospitalized

Six point severity ratings are from the 6-point ordinal rating scale eCRFs. Deaths through Day 15 from AE/SAE and subject disposition CRFs are also taken into account.

3.2 Secondary Endpoints

Procedures are from concomitant procedures eCRFs. Deaths are determined from the following eCRFs: 6-point ordinal severity rating scale; AE/SAE; and subject disposition.

3.2.1 Key Secondary Endpoints

1. Proportion of subjects who have a 6-point severity rating of 5 or 6, are alive, and do not use supplemental oxygen as a procedure at Day 29.
2. Proportion of subjects who have a 6-point severity rating of 2 or 3, or use any ventilation or high-flow nasal cannula as procedures, on any day through Day 29.
3. Proportion of subjects admitted into an ICU on any day through Day 29 from AE/SAE eCRFs.

3.2.2 Other Secondary Endpoints

1. Number of subjects with deaths, SAEs, severe AEs, and Grade 3 or 4 laboratory test abnormalities at any time on study. All AEs are from AE/SAE eCRFs. Grade 3 or 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria defined in the SAP (e.g., CTCAE) from laboratory test eCRFs.
2. Number and percentage of subjects with severe or life-threatening bacterial, invasive fungal, or opportunistic infections at any time through Day 29 from AE/SAE eCRFs.

3. Number and percentage of subjects with intranasal administration reactions at any time through Day 29 from AE/SAE eCRFs.

4. Proportion of subjects with ≥50% reduction in eGFR from baseline at any time on study from laboratory test eCRFs.

4 STUDY PLAN

4.1 Study Design and Duration

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 drug will be zavegepant or matching placebo, given as 10 mg IN dose every 8 hours (+/- 2 hours) for approximately 14 days (42 doses). The study will randomize approximately 120 subjects in a 2:1 ratio across the two treatment groups (zavegepant or matching placebo). The randomization will be stratified by age (less than 60 years vs 60 years and older).

After signing informed consent and meeting eligibility criteria, the subject may be immediately randomized and dosed with the double-blind study medication (10 mg or matching placebo) and continue dosing every 8 hours (Q8h +/- 2 hours) up to approximately 14 days (42 doses).

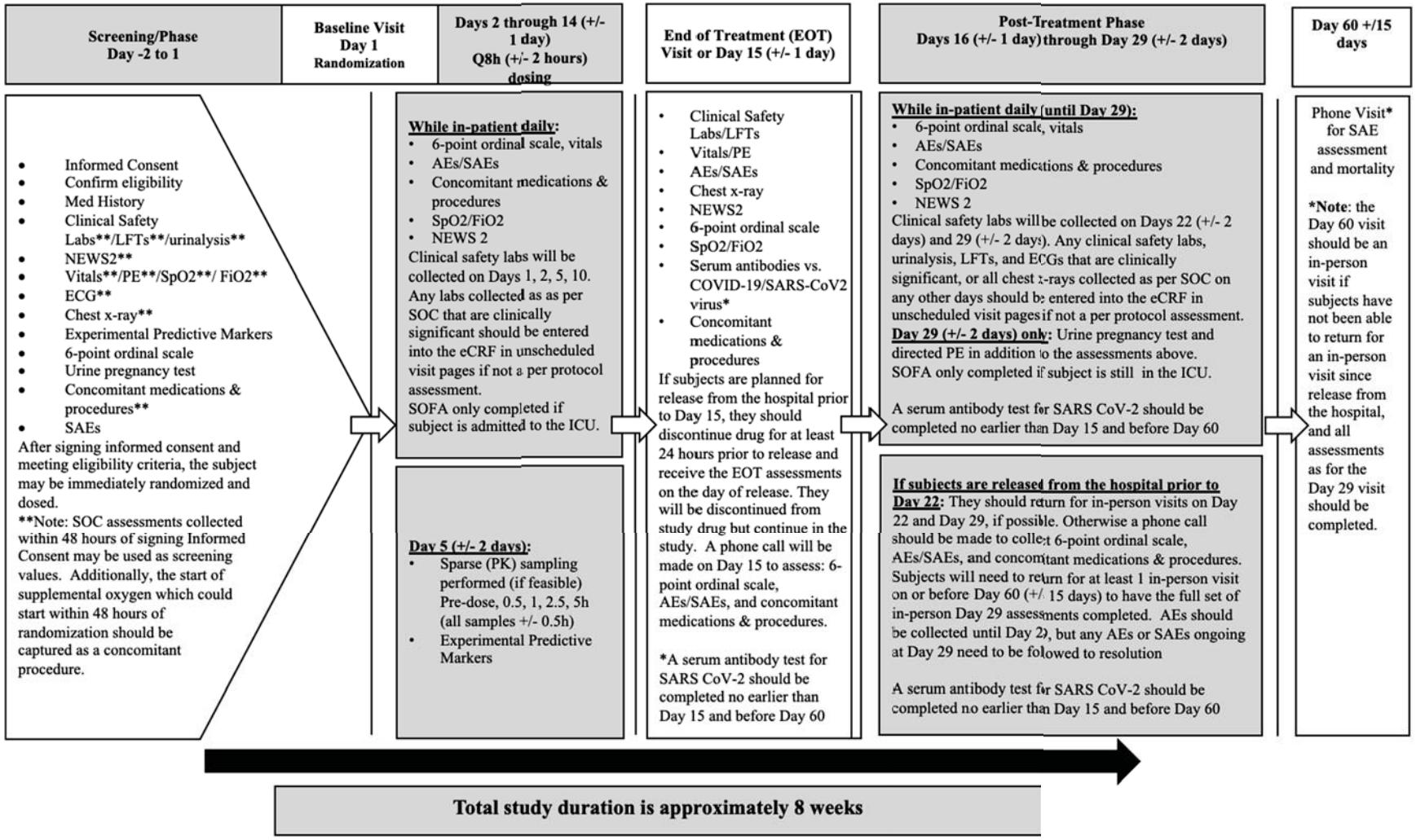
For the purposes of this protocol, the start of Visit Day 1 will start when the 1st dose of study drug is administered until 24 hours later. Therefore, depending on the time when the 1st dose of study drug is administered, a visit day may spread over 2 calendar days. The last dose of study drug could be administered on Visit Day 14 but could actually occur on calendar day 15 of the study. The EOT or Day 15 assessments (depending on when subject stops study drug) should be completed after the last dose of study drug, and the subjects should remain in the hospital for a full 24 hours after their last dose of drug if they are to be released.

Randomization will be done through an IWRS that will be accessed by the unblinded research pharmacists or their designees. so that subjects can be dosed as soon as possible following consent and assessment of eligibility criteria. After completion of treatment, subjects will be followed out to Day 60 (+/- 15 days) during the post treatment phase.

This study has a duration approximately 8 weeks from time of Screening and obtaining consent through the Post-Dose Follow-up Visit (Day 60 +/- 15 days).

4.2 Study Schematic

Figure 2: BHV3500-203 Study Design



4.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
Informed Consent	X						
Inclusion / Exclusion Eligibility Criteria	X	X					COVID-19 test should be positive by PCR test prior to study entry.

[1] If subjects are planned for release from the hospital prior to Day 15, they should discontinue drug for at least 24 hours and receive the End of Treatment assessments prior to discharge. They will be discontinued from study drug but continue in the study. All early discontinuations should be discussed with the Medical Monitor prior to planned release. Subjects will have follow-up phone calls on Days 15, 22, and 29 to assess 6-point ordinal scale, AEs/SAEs, and concomitant medications & procedures unless they are able to return for in-person visits. Subjects will need to return for at least 1 in-person visit on or before Day 60 to have the complete set of Day 29 assessments completed.

[2] EOT assessments should be completed after the last dose of study drug is administered and prior to hospital discharge. If the subject remains in the hospital and completes treatment (42 doses), Day 15 assessments are the same as EOT assessments. If the subject has EOT assessments completed prior to Day 15, then the Day 15 visit is a telephone visit.

[3] After the Treatment Phase, if subjects remain in the hospital or are moved to a recovery facility, subjects should be evaluated **daily** for NEWS2, vitals, concomitant medications, AE/SAE, and SpO2 and FiO2 out to Day 29 with clinical labs collected per protocol on Days 22 and 29. Any clinical safety labs, urinalysis, LFTs, ECGs, or chest x-rays collected as per SOC should be entered into the eCRF in unscheduled visit pages for that assessment if not a per protocol assessment. If subjects are released from the hospital prior to Day 22, they should return for in-person visits on Day 22 (+/- 2 days) and Day 29 (+/- 2 days), if possible, and have a follow-up telephone visit at Day 60. If subjects are unable to return, then follow-up phone calls should be made on Days 22 (+/- 2 days) and 29 (+/- 2 days) to assess 6-point ordinal scale, AEs/SAEs, and concomitant medications and procedures. Subjects will need to return for at least 1 in-person visit on or before Day 60 to have the complete set of Day 29 in-person assessments completed.

Procedure	**Screening Visit Day -2 to Day 1**	**Baseline Visit (Randomization) Day 1**	**Days 2 through 14 (+/- 1 day)[1]**	**End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]**	**Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)**	**Day 60 (+/- 15 days)**	**Comments**
Medical History	X						COVID-19 symptoms should be entered into medical history.
Physical Examination (PE)	X			X	X		Full Physical exam at screening and EOT. If a full PE is collected as per SOC within 48 hours prior to signing Informed Consent, this can be used as the Screening assessment. Directed PE on Day 29 (only).
Urinalysis (pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose and blood)	X						Urinalysis will be collected per protocol at the Screening Visit. Urinalysis values collected within 48 hours of signing Informed Consent may be used as the Screening assessments. If urinalysis is collected as per SOC on any other days from Day 1 through Day 29 and clinically significant, these values should be entered into the eCRF on Unscheduled Visit Urinalysis pages.

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
Clinical Safety Laboratory Testing (Hematology: Hemoglobin, hematocrit, RBC count, WBC count with differentials, and platelets HbA1c Chemistry: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN, serum creatinine, total protein, albumin, uric acid, LDH, and CK	X		X	X	X	X	Clinical safety labs collected within 48 hours of signing Informed Consent may be used as the Screening assessments. Clinical safety labs will be collected per protocol on Days 1, 2, 5, 10, 15, 22, and 29. If clinical safety labs are collected as per SOC on any other days and are clinically significant, these values should be entered into the eCRF on Unscheduled Visit Clinical Safety Labs pages. After hospital discharge, clinical safety labs should be done at in-person visits on Days 22, 29, and 60 (if this is an in-person visit). Abnormal laboratory test values related to an SAE should continue to be recorded out to Day 60.

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
eGFR)							
Electrocardiogram (ECG)	X						ECG will be collected per protocol at the Screening Visit. If an ECG is collected as SOC within 48 hours of signing Informed Consent, it may be used as the Screening ECG. If ECGs are collected as per SOC on any other days from Day 1 through Day 29 and are clinically significant, these values should be entered into the eCRF on Unscheduled Visit ECG pages.
Physical Measurements	X				X		Screening, Day 22 (+/- 2 days) and Day 29 (+/- 2 days) only. Physical measurements collected within 48 hours of signing Informed Consent may be used as the Screening assessments. Height collected at screening only.
Sequential Organ Failure			X	X	X		This is completed only if the subject is admitted to the ICU. It should only be

Procedure	**Screening Visit Day -2 to Day 1**	**Baseline Visit (Randomization) Day 1**	**Days 2 through 14 (+/- 1 day)[1]**	**End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]**	**Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)**	**Day 60 (+/- 15 days)**	**Comments**
Assessment (SOFA)[4]							completed upon ICU admission and at Day 29 if the patient is still in the ICU.

[4] The Sequential Organ Failure Assessment Score (SOFA) will be completed as a supplemental assessment (not part of a scheduled visit) if the subject is admitted to the ICU during the course of the study. The Glascow Coma scale is part of the SOFA assessment and should be completed along with the SOFA assessment.

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
National Early Warning Score (NEWS2) assessment	X		X	X	X	X	NEWS2 assessments collected as per SOC within 48 hours of signing Informed Consent may be used as the Screening assessments. NEWS2 assessments will be collected daily while subject is in the hospital. This assessment may be assessed in the AM or PM but around the same time every collection day within 3 hours and entered on the eCRF. NEWS2 is a collection of ongoing vitals related to: respiration (breaths/min), SpO2 Oxygen saturation (%), BP, pulse, consciousness, temperature to provide a total NEWS2 score. The timing of the NEWS2 for the purpose of the eCRF in the study should also correlate timing with the collection of the SpO2 and FiO2. After hospital discharge, NEWS2 should be collected at in-person visits on Days 22, 29, and 60 (if this is an in-person visit).
Vital Signs	X	X	X	X	X	X	Vital signs collected as per SOC

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
							within 48 hours of signing Informed Consent may be used as the Screening assessment. While subjects are in the hospital, vital signs will be collected once daily in the AM or PM but around the same time every day within 3 hours and entered on the eCRF. After hospital discharge, vital signs should be collected at in-person visits on Days 22, 29, and 60 (if this is an in-person visit).
SpO2 and FiO2	X	X	X	X	X	X	SpO2 and FiO2 collected as part of SOC within 48 hours of signing Informed Consent may be used as the Screening assessments. While the subject is in the hospital, this is collected in the eCRF once daily and should correlate (AM or PM) with the time the vital signs and the NEWS2 are collected. After hospital discharge, SpO2 and FiO2 should be collected at any in-person visits on Days 22, 29, and 60 (if this is an in-person visit).

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
Arterial Blood Gas (ABG)							Arterial Blood Gas (ABG) is not a required assessment for the protocol. However, if it is collected as per SOC within 48 hours from signing Informed Consent through Day 29, this data should be entered in the eCRF in Unscheduled Visit ABG pages.
6-point ordinal scale	X	X	X	X	X	X	While in the hospital, this is collected once daily. This may be collected in the AM or PM at the discretion of the Investigator or staff but should be collect around the same time (within 3 hours) every day. If subjects are discharged from the hospital and unable to return for in-person visits, this scale should be assessed by phone on Days 15, 22, and 29. After hospital discharge, this assessment should be collected at in-person visits on Days 22, 29, and 60 (if an in-person visit).

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
Chest x-ray	X			X			Chest x-ray required at screening and End of Treatment or Day 15 (if subject is in the hospital on Day 15). If a chest x-ray is collected within 48 hours of signing Informed Consent, this may be used as the Screening chest x-ray assessment. If a chest x-ray is collected as per SOC after Day 15 until Day 29, these data should be entered into the eCRF on Unscheduled Visit Chest x-ray pages.
Serum antibody test for SARS-CoV2 virus				X	X		The serum antibody test should be done no earlier than Day 15 and before Day 60
CCI [redacted]	[redacted]		[redacted]				[redacted]

Procedure	Screening Visit Day -2 to Day 1	Baseline Visit (Randomization) Day 1	Days 2 through 14 (+/- 1 day)[1]	End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]	Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)	Day 60 (+/- 15 days)	Comments
							Screening Visit
Liver function tests (LFTs) (AST, ALT, alkaline phosphatase, and bilirubin -Total, Direct, Indirect)	X			X			LFTs will be collected per protocol at the Screening Visit and on Day 15. If LFTs are collected as per SOC within 48 hours of signing Informed Consent, these may be used as the Screening values. If additional LFTs are collected as per SOC on any other days from Day 1 through 29 and are clinically significant, these values should be entered into the eCRF on Unscheduled Visit LFT pages.
Pregnancy Test for women of childbearing potential (WOCBP)	X			X	X Day 29 only	X	Urine test is recommended, but serum may also be done if preferred by Investigator/Staff. WOCBP must have a negative pregnancy test at the Screening Visit before being randomized and treated with IP. If a WOCBP is discharged from the hospital prior to Day 22, a urine pregnancy test should be collected at in-person visits on Days 22 (+/- 2 days), 29 (+/- 2 days), and 60 (+/- 15 days) (if an in-person visit).

Procedure	**Screening Visit Day -2 to Day 1**	**Baseline Visit (Randomization) Day 1**	**Days 2 through 14 (+/- 1 day)[1]**	**End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]**	**Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)**	**Day 60 (+/- 15 days)**	**Comments**
Sparse PK sampling			X Day 5 (+/- 2 days)				PK sampling should be obtained on Day 5 (+/- 2 days). PK may include samples collected at Pre-dose, 0.5, 1, 2.5 and 5h (all samples collected within +/-0.5h).
Concomitant Medication Collection	X	X	X	X	X		Concomitant medications are captured from first dose of study drug through Day 29.
Concomitant Procedures Collection	X	X	X	X	X		Concomitant procedures are captured from first dose of study drug through Day 29 except for the start of supplemental oxygen which could start within 48 hours of randomization. This data should be captured on the concomitant procedures page.
AE Assessment		X	X	X	X		Non-serious AEs are captured from first dose of study drug through Day 29. Non-serious adverse events should be followed until conclusion or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that

Procedure	**Screening Visit Day -2 to Day 1**	**Baseline Visit (Randomization) Day 1**	**Days 2 through 14 (+/- 1 day)[1]**	**End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]**	**Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)**	**Day 60 (+/- 15 days)**	**Comments**
							cause interruption or discontinuation of study drug or those that are present at Day 29. **Note: For this study, admission and discharge to the ICU should be captured on the Adverse Event eCRF.**
SAE assessment	X	X	X	X	X	X	SAEs are captured any time after signing consent through the Day 60 visit. All SAEs should be followed until resolution or stabilization.
Administer study drug		X	X				IP is dispensed every 8 hours (+/- 2 hours) during the Treatment Phase for a total of 42 doses. If subjects are discharged from the hospital to home prior to Day 15 they will be discontinued from study drug but continue in the study. **Please note** that due to the potential for rebound from withdrawal of an immunomodulating agent, subjects who are planning to be discharged should be off of study drug for at least

Procedure	**Screening Visit Day -2 to Day 1**	**Baseline Visit (Randomization) Day 1**	**Days 2 through 14 (+/- 1 day)[1]**	**End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]**	**Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)**	**Day 60 (+/- 15 days)**	**Comments**
							24 hours before release from the hospital. If the subject is discharged to a step-down or satellite care facility where they can be monitored for safety, they should continue receiving study drug until completing 42 doses.
Telephone Visits				X	X	X	If subjects are released from the hospital prior to Day 15 , and an EOT visit was conducted, a follow-up phone call should be made on Days 15, 22, and 29 to assess 6-point ordinal scale, AEs/SAEs, and concomitant medications and procedures. If the subject remains in the hospital on Days 15, 22, or 29, telephone visits are not required, but in-person visits should be conducted.

Procedure	**Screening Visit Day -2 to Day 1**	**Baseline Visit (Randomization) Day 1**	**Days 2 through 14 (+/- 1 day)[1]**	**End of Treatment (EOT) Visit or Day 15 (+/- 1 day)[2]**	**Post-Treatment Phase Days 16 (+/- 1 day) through Day 29[3] (+/- 2 days)**	**Day 60 (+/- 15 days)**	**Comments**
Safety Follow-up Visit (Day 60)						X	If subjects have not had an in-person visit from the time of hospital discharge prior to Day 60, the Day 60 visit should be an in-person visit, and the same assessments that would have been collected on Day 29 should be performed. If subjects have been able to have an in-patient or an in-person visit on Day 29, then the Day 60 visit will be done by telephone to collect 6-point ordinal scale, status of any AEs/SAEs ongoing at time of discharge, any new SAEs, and to confirm subject mortality.

4.3.1 Screening Phase (Day -2 to Day 1)

Approximately 180 subjects will be screened in this study.

Subjects with PCR-documented COVID-19 infection that necessitates hospitalization with supplemental oxygen will be considered for this study. The screening phase is 48 hours. Before any study procedures are performed, subjects must sign Informed Consent. However, any clinical labs, urinalysis, LFTs, PE, Vitals, SpO2, FiO2 , NEWS2 assessments, ECG, or chest x-ray collected as per SOC within 48 hours of signing Informed Consent may be used as the Screening assessments.

Concomitant procedures are captured from first dose of study drug through Day 29 except for the start of supplemental oxygen which could start within 48 hours of randomization. This data should be captured on the concomitant procedures page.

After Informed Consent has been signed, subjects will be assessed for eligibility and should be immediately randomized once eligibility is confirmed. Subjects will also undergo all screening procedures prior to randomization, including the collection of Experimental Predictive Biomarkers as detailed in Table 1 and Section 6.3.5.2. If the screening laboratory test results or any eligibility criteria are determined to be unacceptable per protocol, the subject is considered a screen failure and will not be allowed to re-screen for the study.

4.3.2 Baseline Visit / Randomization (Day 1)

The Baseline Visit should occur as quickly as eligibility is confirmed after consent form is signed (and no greater than 48 hours later). An unblinded research pharmacist will be required to dispense medication to the research staff. Screening procedures should be completed as quickly as possible so that the patient is randomized within 48 hours from the start of non-invasive supplemental oxygen. All Baseline Visit procedures are outlined in Table 1.

4.3.3 Treatment Phase (Days 1 – 14 +/-1 day)

Approximately 180 subjects will be screened to randomize approximately 120 subjects. The subjects will be randomized in a 2:1 ratio to the zavegepant (80 subjects) or placebo (40 subjects) treatment groups. Subjects will receive 10 mg IN zavegepant or placebo every 8 hours (+/- 2 hours) for approximately 14 days (42 doses). Subjects whose renal function declines to an eGFR of < 15 mL/min will be discontinued from study drug.

4.3.3.1 While Subjects are In the Hospital

During the Treatment Phase, while subjects are inpatient, SpO2, FiO2 and ongoing vitals will be collected ***each day***. Although these procedures may be collected throughout the day as part of standard of care, for the purpose of data collection for this study, vitals, SpO2, and FiO2 will be collected in the eCRF **one time daily**. This data may be collected in the morning (AM) or evening (PM) but should be around the same time every day (within 3 hours) and entered on the eCRF. Arterial Blood Gas (ABG) is not a required assessment per protocol. However, if ABG

is collected as per SOC at any time within 48 hours prior to signing Informed Consent through Day 29, this data should be entered in the eCRF whenever it is collected on Unscheduled Visit ABG pages.

NEWS2 is a collection of ongoing vitals related to: respiration (breaths/min), SpO2 oxygen saturation (%), blood pressure (BP), pulse, consciousness, and temperature to provide a total NEWS2 score. While subjects are inpatient, NEWS2 should be assessed daily. The timing of the NEWS2 for the purpose of the data collection for the study should also correlate with the timing of the collection of the SpO2 and FiO2, and entered in the eCRF.

Subjects will have SAE/AEs monitored as well as concomitant medications and procedures daily.

Clinical safety labs, urinalysis, LFTs, ECGs, and chest x-rays will be collected as specified in Table 1.

If the subject is admitted to the ICU, then SOFA2 will be collected upon admission to the ICU, and will be collected again if subject is still in the ICU at Day 29.

If during the treatment period, subjects are transferred to another care facility, they should continue on study drug with the expectation that the Investigator and Staff will coordinate with the treating facility to obtain, at minimum, safety and primary endpoint data and allow the subject to complete the trial as per protocol.

For the purpose of the 6-point ordinal primary endpoint scale, item number 6 (Not Hospitalized) means discharged from acute care. Transferring a subject to another acute care facility due to COVID-19 challenges does not qualify as a 6 on the ordinal scale. Any operational questions about logistics of a transferred subject should be addressed with the Biohaven Medical Monitor or designee.

If local administration site irritation develops, the PI should call the medical monitor to discuss the dosing plan.

4.3.3.2 If Subjects are Discharged Prior to Day 15

If a subject is planned to be discharged from the hospital prior to completing treatment, they will be discontinued from study drug. The Investigator should discuss the discharge plan with the Medical Monitor.

Note: **Due to the potential for rebound from withdrawal of an immunomodulating agent, if a subject is withdrawn from drug, they need to be monitored in the hospital for at least 24 hours before release**. All End of Treatment (EOT) assessments (see Section 4.3.5) should be collected after the patient's last dose of study drug and prior to discharge. Although subjects will be discontinued from the study drug, they will remain in the study. If possible, subjects should continue with in-person visits as per Table 1. If this is not possible due to COVID-19 restrictions, a phone call should be made to the subject on Days 15, 22, and 29 to collect these assessments: 6-point ordinal scale, AEs/SAEs, and concomitant medications and procedures. If

the subject is unable to return for in-person visits on Days 22 and 29 due to quarantine, subjects will need to return for at least 1 in-person visit on or before Day 60 to have the Day 29 in-person assessments completed.

4.3.4 Treatment Phase Day 5 (+/- 2 days)

In addition to what is collected daily during the Treatment Phase as per Table 1, whenever possible, sparse PK will be collected on Day 5 (+/- 2 days). Additionally, experimental predictive biomarkers will be collected on Day 5 (+/- 2 days), with the exception of troponin which is only collected at Screening as per Table 1.

4.3.5 End of Treatment or Day 15 (+/- 1 day)

Subjects will complete the End of Treatment (EOT) Visit after their last dose of study drug (if they discontinue drug prior to Day 15) or on Day 15 +/- 1 day after the subject has received 42 doses of study drug as per Table 1. If possible, the subject should return for Post-Dose Follow-up visits on Day 22 (+/- 2 days) and Day 29 (+/- 2 days). If a subject has an EOT visit prior to Day 15, then the Day 15 visit should be done as a telephone visit.

Subjects need to have a SARS CoV-2 antibody test completed no earlier than Day 15, but no later than Day 60 (see Section 6.3.5.4).

4.3.6 Post Treatment Phase (Days 16 +/- 1 day Through 29 +/- 2 days)

4.3.6.1 For Subjects Who Remain in the Hospital

After administration with the study medication ends, the 6-point ordinal scale assessment, daily vital signs, SpO2, FiO2, concomitant medications and procedures, and NEWS2 will continue to be collected daily while the patient is in the hospital (Table 1). AEs/SAEs, should be captured and followed to resolution or stabilization. Clinical safety labs will be collected per protocol on Days 22 (+/- 2 days) and 29 (+/- 2 days). If clinical safety labs, urinalysis, LFTs, and ECGs are collected as per SOC on any days out to Day 29, data that are clinically significant should be entered into the eCRF on Unscheduled Visit assessment pages. Any chest x-rays collected as per SOC from Day 16 through 29 should be entered into the eCRF on Unscheduled Visit Chest x-ray pages.

If the subject is admitted to the ICU, then SOFA2 will be collected upon admission to the ICU and on Day 29 if the subject is still in the ICU. Subjects need to have a SARS CoV-2 antibody test completed no earlier than Day 15, but no later than Day 60 (see Section 6.3.5.4).

4.3.6.2 For Subjects Discharged from the Hospital after Day15, but Prior to Day 22

If a subject is discharged from the hospital prior to Day 22, when possible, they should return to the site on Day 22 (+/- 2 days) and Day 29 (+/- 2 days) to have the assessments indicated in Table 1 and should receive a follow-up phone visit on Day 60.

If the subject is unable to return for in-person visits on Days 22 and 29 due to COVID-19 restrictions, a phone call should be made to the subject to collect these assessments: 6-point ordinal scale, AEs/SAEs, and concomitant medications and procedures on those visit days (+/- 2 days). Subjects will need to return for at least 1 in-person visit on or before Day 60 to have the Day 29 assessments completed. Subjects need to have a SARS CoV-2 antibody test completed no earlier than Day 15, but no later than Day 60 (see Section 6.3.5.4).

4.3.7 60-Day Safety Follow-up Visit (+/- 15 Days)

If subjects have been able to return for an in-person visit on Day 29, this will be a follow-up safety phone visit. During this contact, the staff will collect the 6-point ordinal scale, collect any new SAEs, update the status of any AE/SAEs that were ongoing since the last visit, and confirm subject mortality status.

If subject has been unable to complete an in-person visit from the time of hospital discharge prior to Day 60, this Day 60 visit should be an in-person visit, and the same assessments that would have been collected at Day 29 should be performed.

4.4 Post Study Access to Therapy

Not Applicable.

5 POPULATION

Individuals entered in this trial will be male and female subjects 18 years of age and older with PCR-documented COVID-19 infection that necessitates hospitalization with supplemental oxygen. The treatment setting for these subjects will include hospitals or institutions where subjects will be treated for symptoms related to COVID-19. Subjects may be recruited through a variety of sources, including referrals from physicians and other health care professionals.

5.1 Number of Subjects

Up to approximately 180 subjects will be screened and up to approximately 120 subjects will be treated with study drug in this study. It is anticipated that enrollment will occur at approximately 2-5 sites in the United States over a period of approximately 4 months.

5.2 Inclusion Criteria

1. Subjects must provide informed consent in accordance with requirements of the study center's IRB or ethics committee, prior to the initiation of any protocol-required procedures.

2. Subjects must agree to provide all requested demographic information (i.e. gender, race).

3. Subjects must be able to read and understand English or Spanish.

4. Subjects must be over the age of 18 years.

5. Subjects must have laboratory-confirmed SARS-CoV-2 infection as determined by PCR-based commercial or public health assay.

6. Subjects must have symptoms that require hospitalization with supplemental oxygen and/or non-invasive ventilation as determined by the admitting physician. The maximum nasal cannula O_2 concentration should be determined by the treating clinician and the limitations of the specific equipment.

7. Subjects must be willing and able to comply with study-related procedures/assessments.

5.3 Exclusion Criteria

1. Subjects in immediate need of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

2. Subjects with an eGFR of < 30 mL/min, at the Screening Visit

3. Prisoners or subjects who are involuntarily incarcerated

4. Subjects who are participating in any other investigational clinical trial while participating in this clinical trial

5. Subjects who are under the age of 18 years

6. Subjects who are pregnant (all potential female enrollees need to have a negative pregnancy test prior to IP administration)

7. Subjects with multi-organ failure

8. Subjects who have received more than 48 hours of supplemental oxygen prior to randomization

9. Subjects with prior significant pulmonary disease (e.g., severe COPD/ILD/CHF/IPF) are excluded

10. Subjects receiving investigational therapies as part of a formal clinical trial for the treatment of COVID-19. During the course of this study, investigational therapies that may become "standard of care" to treat COVID-19, but are not part of a clinical trial, are allowed.

11. Subjects who are on long-acting CGRP monoclonal antibodies will be excluded including Aimovig® (erenumab), Emgality® (galcanezumab), Ajovy® (fremanezumab), and Vyepti® (eptinezumab). Additionally, the investigational oral CGRP receptor antagonist, atogepant, that is taken daily will also be excluded. Oral CGRP receptor antagonists, Nurtec® ODT (rimegepant) and Ubrelvy™ (ubrogepant) that are typically used PRN infrequently will not be excluded as long the subject was not taking them on a daily basis and does not take them during the current study

12. Subjects who are unlikely to survive for more than 48 hours from the Screening Visit

13. Subjects with any of the following abnormal laboratory values at screening: aspartate AST or ALT greater than 5x ULN or bilirubin greater than 2x ULN

14. Subjects with known active TB, history of incompletely treated TB, suspected or known extrapulmonary TB

15. Subjects with suspected or known systemic bacterial or fungal infections. However, empiric antibiotics are permitted

16. Subjects who have participated in any clinical research study evaluating an IP or therapy within 3 months and less than 5 half-lives of IP prior to the screening visit

17. Subjects with any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study

Please see Section 5.4 for prohibited medications during the course of the study.

5.4 Prohibited and Restricted Concomitant Medications/Procedures

Investigational therapies as part of a formal clinical trial for the treatment of COVID-19 are prohibited during the course of this study. However, if during the course of this study investigational therapies become "standard of care" to treat COVID-19, they are allowed.

Long-acting CGRP monoclonal antibodies Aimovig (erenumab), Emgality (galcanezumab), Ajovy (fremanezumab), and Vyepti (eptinezumab) are not allowed in the trial. A minimum 30-day washout period for these drugs is appropriate, prior to randomization. Additionally, the investigational oral CGRP receptor antagonist, atogepant, that is taken daily will also be excluded. Oral CGRP receptor antagonists, Nurtec ODT (rimegepant) and Ubelvy (ubrogepant) that are typically used PRN infrequently will not be excluded as long the subject was not taking them on a daily basis and does not take them during the current study.

Prior to the Baseline Visit (randomization), if a subject has been on non-invasive supplemental oxygen for more than 48 hours, they should not be randomized. However, if a subject progresses to requiring mechanical ventilation (invasive or non-invasive) after randomization, they will remain on the study, per the Investigator's judgement.

Subjects with renal impairment who have an eGFR2. 30mL/min are allowed into the study. Subjects who develop an eGFR< 15mL/min while on the study should be discontinued from the study drug.

5.5 Women of Childbearing Potential

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Menopause is defined as:

- Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL

  Or

- Woman with irregular menstrual periods and a documented serum FSH level > 35mIU/mL

  Or

  NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to one year

- Woman on hormone replacement therapy (HRT)

For the purpose of this study, subjects who are WOCBP, MUST have a negative pregnancy test prior to randomization and administration of study medication. If during the course of the trial the subject is discharged for the remainder of the study, the subject should be abstinent and/or

use an acceptable method of birth control if they become sexually active. Acceptable methods of birth control are listed below.

- WOCBP and all men must use acceptable methods of contraception to avoid pregnancy throughout the study and for 90 days after the last dose of investigational product in such a manner that risk of pregnancy is minimized. The requisite drug interaction studies to determine the interaction of zavegepant with oral contraceptives have not been performed to date. It is, therefore, not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP or men with partners who are WOCBP who are participating this study. Oral estrogen and progestin hormonal contraceptives as a sole method of contraception are therefore prohibited.

- It is required that all WOCBP use two methods of contraception to prevent pregnancy, for the duration of the study (i.e. this study begins with signed consent form through 90 days after last dose of study drug). The two methods should include one barrier method (ex. condom with spermicidal gel, intrauterine devices, cervical cap etc.) and one other method. The other method could include hormonal contraceptives (e.g. oral contraceptives, injectable contraceptives, patch, or contraceptive implant) used since at least 4 weeks prior to sexual intercourse or another barrier method.

- Subjects who report abstinence, or who report exclusively being in same-sex relationships are still required to comply with the contraception requirements in this study to prevent pregnancy. These subjects must still be counseled on the requirement to avoid pregnancy throughout the study and for 90 days after the last dose of study medication, as well as acceptable methods of contraception to use during the study.

- All WOCBP must complete the pregnancy test schedule (Table 1).

- Male subjects must be willing not to donate sperm until 90 days following the last study drug administration.

5.6 Other Restrictions and Precautions

Not Applicable.

5.7 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion/exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by your IRB/EC. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

The following study materials will be provided to the site:

- Investigator File/Study Binder
- Drug Accountability Logs (blinded and unblinded)
- IB
- eCRF Completion Instructions
  - eCRFs will be prepared for all data collection fields
- Drug Administration Instructions
- Laboratory manual, laboratory kits for PK and labels for CGRP samples will be provided. PK samples and CGRP samples will be shipped to a central laboratory for analysis
- Local laboratory collection will be used for this study and performed via hospital procedures for all labs with the exception of any experimental biomarkers that local labs are not able to perform (see Section 6.3.5.2)
- Experimental Predictive Biomarkers Collection and Processing Instructions. For experimental biomarkers that cannot be done at the local lab, instructions have been provided to order tests through a central laboratory for analysis and reporting.
- SAE Forms and SAE instructions
- Pregnancy surveillance forms and reporting instructions
- Instructions for NEWS2 and SOFA assessments for data entry

6.2 Eligibility Assessments

Informed consent, inclusion/exclusion criteria including medical history, concomitant medications and procedures, and laboratory assessments should be completed as outlined in Table 1. Any eligibility assessments completed within 48 hours of signing Informed Consent may be used as the Screening assessments. The start of non-invasive supplemental oxygen should be captured on the concomitant procedures page.

6.3 Safety Assessments

6.3.1 Vital Signs and Physical Measurements (Height and Weight)

Body weight and height will be recorded at the scheduled visits as outlined in Table 1. While in the hospital, vital signs and SpO2, and FiO2 will be collected daily and entered into the eCRF. The site staff should collect this around the same time every day within 3 hours, and the collection for the purpose of data entry into the eCRF should correlate to the time the NEWS2 is collected (AM or PM). Vital signs, SpO2 and FiO2, and NEWS2 assessments should be done at any in-patient or in-person visit up to Day 60. Although not a required protocol assessment, If ABG is collected from Screening through Day 29 as per SOC, this data should be entered in the eCRF in Unscheduled Visit ABG pages whenever it is collected.

6.3.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be collected per protocol at the Screening Visit. If an ECG is collected as per SOC within 48 hours of signing Informed Consent, this may be used as the Screening ECG. If ECGs are collected as per SOC on Days 1 through 29, these values should be entered into the eCRF in Unscheduled Visit ECG pages if they are determined to be clinically significant. The Investigator will determine if any abnormalities are of clinical significance.

6.3.3 Chest x-ray

A standard chest x-ray will be recorded at the screening visit and at the EOT or Day 15 visit as per Table 1. A chest x-ray collected within 48 hours of signing Informed Consent may be used as the Screening chest x-ray. If a chest-x-ray is collected as per SOC after Day 15 out to Day 29, the data should be collected in the eCRF in Unscheduled Visit Chest x-ray pages. The Investigator will determine if any abnormalities are of clinical significance.

6.3.4 Physical Exam

Subjects will undergo a physical examination (PE) at the scheduled visits as outlined in (Table 1). If a full PE is performed within 48 hours of signing Informed Consent, it may be used as the Screening PE. The directed physical exam should be guided by the subject's signs and symptoms.

6.3.5 Laboratory Assessments

The investigator must review all laboratory reports, document this review, and record any clinically significant relevant changes occurring during the study in the AE section of the eCRF (see guidance in Section 8.4.2). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory test findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with abnormal values collected through Day 29 considered to be clinically significant by the Investigator should be reported as adverse events and repeated and recorded in the eCRF until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. Abnormal laboratory test values related to an SAE should continue to be recorded out to Day 60.

If such values do not return to normal/baseline within a reasonable period of time judged by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with Table 1.

If laboratory values from non-protocol specified laboratory assessments performed as per SOC require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

6.3.5.1 Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Table 1 for clinical laboratory evaluations. If clinical labs are collected within 48 hours of signing Informed Consent, they may be used as the Screening labs. Laboratory samples will be collected and processed via hospital/site standard operating procedure (SOP).

Clinical Safety Labs:

- **Hematology**: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count, and differentials (neutrophils, basophils, eosinophils, lymphocytes, monocytes, bands)
- **HbA1c**
- **Chemistry**: albumin, calcium, creatinine kinase (CK), serum glucose, LDH, total protein, potassium, sodium, uric acid, blood urea nitrogen (BUN), serum creatinine, chloride, and bicarbonate
- **eGFR and method of calculation**

LFTs:

- AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, and indirect bilirubin

Urinalysis:

- pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, urine protein, urine glucose, and blood

CCI [redacted]

[redacted]

[redacted]	[redacted]		
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[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

CCI [redacted]

6.3.5.4 SARS-CoV-2 Antibody Testing

The serum antibody test should be done no earlier than Day 15 and before Day 60. The test should be performed by the hospital local lab or can be sent to a Central Lab if an account has been set-up by the Sponsor for the site.

6.3.5.5 Pregnancy Testing

Pregnancy tests will be conducted (serum or urine), when appropriate and as outlined in Table 1.

6.4 Efficacy Assessments

6.4.1 6-point ordinal scale

A 6-point ordinal scale will be collected for the Primary and secondary endpoints. The scale consists of the following anchor points:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen
6. Not hospitalized

The 6-point ordinal scale will be collected each day the subject is in the hospital and at all in-person or telephone visits.

6.5 Other Assessments

6.5.1 National Early Warning Score (NEWS2)

The NEWS2 is a validated tool for assessing physiological risk in deteriorating subjects and is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when subjects present to, or are being monitored in the hospital.[45] Six simple physiological parameters form the basis of the scoring system: 1) respiration rate; 2) oxygen saturation; 3) systolic blood pressure; 4) pulse rate; 5) level of consciousness or new confusion; and, 6) temperature.

6.5.2 Sequential Organ Failure Assessment (SOFA) Score

The (SOFA score, previously known as the sepsis-related organ failure assessment score, is used to track a person's status during the stay in an ICU to determine the extent of a person's organ function or rate of failure[8,46-51]. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. The higher the SOFA score, the higher the likely mortality.

6.5.3 COVID-19 Characteristics and Outcomes

Biohaven will collect several data points to better understand the current COVID-19 characteristics and outcomes with regard to how hospitals are managing in the current environment secondary to this disease. The datapoints will include (but not limited to) the following:

- When collecting SAEs with an outcome of death, collect whether the death occurred after withdrawal of care, and if so the reason for withdrawal of care
- Supportive measures received by subjects who progress to ARDS within the study (e.g., proning, paralytics etc.)
- Data collection on clinical decision-making that guides removal of a subject from mechanical ventilation in relation to their clinical deterioration or lack of clinical response (e.g., change in status to comfort measures, poor prognosis for recovery, allocation of resources in a pandemic setting etc.)
- Collection upon study entry of reason for hospital admission, standard of care followed for each subject at a site and if care decisions are made based on resource limitation
- Collection of any new infection that occurs during the study, (i.e., viral or non-viral), including the site of infection and source of culture (BAL, Tracheal aspirate, sputum, blood, urine etc.)
- Collect the number of days between onset of symptoms and initiation of treatment with zavegepant

6.6 Early Discontinuation from Investigational Product

Subjects must discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Subject's eGFR decreases to < 15 mL/min
- Subjects who are discharged from the hospital prior to completing the treatment period

All subjects who discontinue treatment should still comply with remaining study visits and procedures as outlined in Table 1.

6.7 Early Discontinuation from the Study

Subjects must discontinue investigational product and withdraw from the study for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator or sponsor, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Biohaven Pharmaceuticals

All subjects who terminate early (e.g., AE discontinuation) should still comply with remaining study visits and procedures as outlined in Table 1, and Section 4.3.6.2. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (as defined above).

6.8 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

An IP is defined as follows:

- A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, IP is/are:

- Zavegepant 10 mg IN and will be provided as single use disposable Aptar UDS devices fully prepared and ready for administration

- Matching placebo IN devices provided as single use disposable Aptar UDS devices fully prepared and ready for administration

7.1.2 Non-Investigational Product

Other medications used as support or rescue medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are:

Not Applicable

7.1.3 Formulation

Zavegepant (BHV-3500), is formulated as 10 mg IN for intranasal single dose administration using an Aptar Unit Dose System (UDS) liquid spray device

7.1.4 Packaging, Shipment and Storage

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. Please see the IB for specific conditions. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the Sponsor/Clinical Research Organization (CRO) immediately.

7.2 Dose and Administration

Subjects who are hospitalized will be administered three doses (IN devices) per day of blinded IP (10 mg or matching placebo) to be dosed approximately 8 hours (+/- 2 hours) apart, for up to 14 days (42 doses) of treatment. When possible, if subjects are discharged from the hospital to another acute care medical facility prior to completing treatment, they will be provided with enough of their blinded IP and dosing instructions to continue their Q8h regimen until 42 doses have been completed.

Subjects who are discharged to home prior to completing treatment will be discontinued from study drug. Procedures indicated in Section 4.3.3.2 should be followed.

7.2.1 Method of Assigning Subject Identification

Randomization will be done through an IWRS, that will be accessed by the unblinded research pharmacists or their designees. The randomization scheme will be stratified by age (<60, 2. 60).

Initially, after informed consent is obtained at the Screening Visit, the Investigator or designee will enter the subject into the study and assign a patient ID (PID). The PIDs will be sequentially assigned within each site, and will have the format XXX-YYYY, where XXX is the 3 digit site number and YYYY is the sequential subject number.

Sites will be responsible for recording the container numbers dispensed to the subject on the Drug Accountability Form provided in the Regulatory Binder, as well as ensure appropriate documentation of dispensation in the subject's medical record.

7.2.2 Selection and Timing of Dose and Administration

Subjects, study staff, or hospital floor staff will be instructed to administer one spray from a single device three times per day at approximately 8 hours (+/- 2 hours) apart between doses. If possible, alternate nostrils should be used for each subsequent dose. Dosing will continue for up to 14 days (42 doses). For the purposes of this protocol, the start of Visit Day 1 will start when the 1st dose of study drug is administered until 24 hours later. Therefore, depending on what time the 1st dose of study drug is administered, a visit day may spread over 2 calendar days. The last dose of study drug could be administered on Visit Day 14 but could actually occur on calendar day 15 of the study.

7.3 Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician.

Before breaking the blind of an individual subject's treatment, the Investigator should have determined that the information is necessary, (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

A pharmacokineticist, unblinded site monitor, unblinded site pharmacist, Biohaven Drug Supply Coordinator and pharmacovigilance designees may be unblinded before data are unblinded for the primary endpoint and all subjects complete the study. Except as noted above, other members of the BHV research team will remain blinded. For purposes of the DMC, periodic analysis will be carried out by the unblinded safety biostatistics team independent and firewalled from the team directly involved with the design and primary analysis of the trial. A report will be prepared for the DMC as outlined in the DMC charter.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind for remaining site personnel.

7.4 Treatment Compliance

Responsible study personnel or hospital floor staff will dispense the study drug to the study subjects. Accountability and compliance verification should be documented in the subject's study records. For subjects discharged to another care facility, treatment compliance and drug accountability should be continued.

Missed doses should be documented in the subject source/medical record. Since this study is intended to take place in the hospital setting, it is imperative that missed doses are correctly accounted for in addition to any intentional or unintentional dosing errors.

7.5 Destruction and Return of Study Drug

All unused study drug can be sent back to the drug depot for destruction only after being inspected and reconciled by the responsible Study monitor or the sponsor's designee. If it is site policy to destroy study drug on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor or the Sponsor's designee.

8 ADVERSE EVENTS

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example) symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during an open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

If a specific diagnosis or syndrome is identified by the Investigator, this should be recorded as the AE, rather than recording (as separate AEs) the individual signs/symptoms or clinically significant laboratory test abnormalities known to be associated with and considered by the Investigator to be a component of the disease/syndrome.

Note: For this study, all admissions and discharges to and from the ICU need to be captured on the Adverse Event eCRF.

8.1 Definition of Terms Related to all Adverse Events (Serious and Non-serious)

Mild: Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Severe: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything, untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

8.2 Assessment for Determining Relationship of AE to Study Drug

The relatedness of each AE to study drug must be classified based on medical judgement and according to the following categories. The definitions are as follows:

Related: This category applies to AEs that are considered, with a high degree of certainty, to be related to the study drug. An AE may be considered related when it follows a temporal sequence from the administration of study drug, it cannot reasonably be explained by the known characteristics of the subject's clinical state, environment, or toxic factors, or other modes of therapy administered to the subject. An AE may be considered related when it follows a known pattern of response to the study drug, or if the AE reappears upon re-challenge.

Possibly related (non-serious AEs only): This category applies to AEs that are considered to have an unlikely connection to study drug, but a relationship cannot be ruled out with certainty.

Unlikely related (non-serious AEs only): This category applies to AEs that do not follow a reasonable temporal sequence from the administration of the study drug. The AE may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Unrelated: This category applies to AEs that are considered with a high degree of certainty to be due only to extraneous causes (e.g. subject's clinical state, environment, toxic factors, disease under study, etc.) and does not meet the criteria of other categories above.

There are two types of adverse events, Serious Adverse Events (SAE) and Non-Serious Adverse Events (AEs).

8.3 Serious Adverse Events

8.3.1 Definition of Serious Adverse Event (SAE)

In general, an SAE is any event that meets any of the following criteria listed below regardless of the relationship to study drug:

- Death
- Life-threatening
- Prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received zavegepant
- Other: Important medical events such as admission to ICU because of worsening of subject's condition, intubation or other medical procedures performed because of worsening of subject's condition, etc.

- Other important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse
    - Potential drug induced liver injury (see Section 8.3.5)
    - Abuse or Overdose of medication
        - Potential study medication abuse (including cases of excessive non-compliance with study medication dosing instructions or subjects who discontinue treatment without returning study medication) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor subjects for possible cases of abuse of study medication (subjects taking study drug for non-therapeutic purposes, e.g. for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies
        - Potential study medication overdose is defined in Section 8.3.3

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

The following hospitalizations are not considered SAEs in Biohaven clinical studies (but may be considered non-serious AEs):

- A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life threatening);
- Elective surgery planned prior to signing consent;
- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission (i.e., routine colonoscopy);
- Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (i.e., lack of housing, care-giver respite, family circumstances).

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

8.3.2 Collection and Reporting Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur from signing consent and throughout the course of the study up to and including the Post-dose Follow-up Visit Day 60.

All SAEs should be followed to resolution or stabilization.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the study drug but is potentially related to the conditions of the study (such as a withdrawal of previous therapy or a complication related to study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, overdose (see Section 8.3.3), potential drug induced liver injury (see Section 8.3.3) and pregnancies (see Section 8.3.4) must be reported within 24 hours of the Investigator becoming aware of the event. The Investigator is responsible for submitting all applicable events to the IRB as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering the SAE information into the eCRF and/or system (i.e., event term, start/stop dates, causality, and severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to PPD Pharmacovigilance (PVG). A written description of any serious adverse event, using the PPD SAE report form, must be sent to PPD PVG by facsimile (fax), within 24 hours after awareness of the event:

- North America: 1-888-488-9697
- **EU EMEA: +44 1223 374 102**

Due to COVID-19 restrictions for sites, SAE reports may be sent via encrypted email to PPD at: wilsafety@ppdi.com. The subject line of the email must include "**Biohaven Protocol BHV3500-203**."

If a form is unable to be submitted within 24 hours, the SAE may be reported by telephone via the Safety Hotline Number:

- North America: 1-800-201-8725
- **EU EMEA: +44 1223 374 240**

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used.

The minimum information required for an initial SAE report is:

- Sender of report (Site number, Investigator name)
- Subject identification (subject number)
- Protocol number
- SAE term (if an SAE is being reported)

8.3.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both **excessive** and **medically important**.

All occurrences of medically significant overdose (suspected or confirmed and irrespective of whether it involved zavegepant) must be communicated to Biohaven or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any treatments administered.

Asymptomatic dosing errors (e.g. accidentally taking two tablets instead of prescribed dose of one tablet in one calendar day) should be reported as deviations.

8.3.4 Pregnancy

If, following the baseline visit, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of the investigational product exposure, including during at least 6 half-lives after the product administration, the investigational product will be permanently discontinued in an appropriate manner (i.e., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Sites should instruct subjects to contact the Investigator if they become pregnant during the course of the study. The investigator must immediately notify the Biohaven (or designee) Medical Monitor and PPD of the event and complete the Pregnancy Form in accordance with SAE reporting procedures as described in Section 8.3.2. The pregnancy should be reported using paper forms, which should be faxed to PPD PVG by facsimile (fax), within 24 hours after Investigator/site awareness of the event:

- North America - 1-888-488-9697

- **EU EMEA: +44 1223 374 102**

Due to COVID-19 restrictions for sites, SAE reports may be sent via encrypted email to PPD at: wilsafety@ppdi.com. The subject line of the email must include "**Biohaven Protocol BHV3500-203**."

Or if the form cannot be faxed or emailed it should be reported via phone to the PPD Safety Hotline at North America: 1-800-201-8725 or EU EMEA: +44 1223 374 240.

Once the paper form is available, the data must be reported per standard procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must also be reported on a Pregnancy Report Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor/PPD. Information on this pregnancy will be collected on the Pregnancy Report Form, as appropriate.

8.3.5 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 8.3.2.

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 times the upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

If any potential DILI is identified and meets the criteria above, the Biohaven Medical Monitor (or designee) should immediately be contacted for further instruction and whether the subject must discontinue from the trial and appropriate follow up requirements.

8.4 Non-serious Adverse Events

A ***non-serious adverse event*** is an AE not classified as serious.

8.4.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the initiation of study drug through Day 29.

Non-serious adverse events should be followed until conclusion or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at Day 29.

8.4.2 Laboratory Test Abnormalities

The following laboratory test abnormalities should be captured on the non-serious AE eCRF page (out to Day 29) or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is determined to be clinically significant or meets the definition of an SAE;
- Any laboratory test abnormality that requires the subject to have the study drug discontinued or interrupted;
- Any laboratory test abnormality that requires the subject to receive specific corrective therapy.

8.5 Adverse Events of Special Interest

Not Applicable.

9 STATISTICS

Complete details on the statistical methods for this study may be found in the Statistical Analysis Plan (SAP).

9.1 Sample Size

This study will randomize 120 subjects in a 2 to 1 ratio, to zavegepant and placebo, respectively.

Since our understanding of the course of the disease as measured by the primary endpoint, 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 II 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 this protocol, some epidemiological data was informally gathered by Biohaven from local hospitals. For 300 subjects tested for COVID-19, the distribution on the primary endpoint was estimated to be as shown in Table 2.

Table 2: Distribution, number (N), and percent (%) of 300 subjects tested for COVID-19

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%

The table shows the distribution at the time of initial testing for a broad range of subjects. 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 data can be described as having a mean of 3.1 and a standard deviation of 1.1.

Based on the table, we speculate that after 14 days of treatment the distribution of subjects on placebo might have a standard deviation as high as 1.5 units. 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 group, and alpha level of 0.05 and a common standard deviation of 1.5 units.

9.2 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
- Randomized: Subjects in the enrolled analysis set who receive a randomized treatment group assignment (zavegepant or placebo)
- Safety: Subjects in the enrolled analysis set who receive at least one dose of study drug (zavegepant or placebo)
- Efficacy: Subjects in the randomized analysis set who are randomized only once, and receive at least one dose of study drug.

9.3 Statistical Methods

Categorical variables are tabulated with counts and percentages. Continuous variables are summarized with univariate statistics (e.g., n, mean, standard error, median, minimum and maximum).

For the calculation of descriptive statistics of observed data, subjects must have a baseline value to be evaluable for endpoints based on values and changes from baseline over time.

Tabulations of the following endpoints present the number of unique subjects with an event: protocol deviations; non-study medications; AEs; and laboratory test abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

9.3.1 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics are made for the efficacy and safety analysis sets.

9.3.2 Primary Endpoint

The primary endpoint will be analyzed using a Mixed Model for Repeated Measures (MMRM) with treatment group, visit, visit-by-treatment group interaction, and randomization stratum age group as fixed effects, baseline SpO2/FiO2 ratio as a covariate, and subject as a random effect. Visit will be a categorical variable based on analysis visit windows for Days 5, 10, 15, 22, and

29. The primary endpoint will be tested by comparing zavegepant to placebo at Day 15 at an alpha level of 0.05. Descriptive statistics will be provided for each treatment group that show the number and percentage of subjects in each category. Analyses are based on the efficacy analysis set.

9.3.3 Secondary Endpoints

If the primary endpoint is significant at alpha :S 0.05, then the key secondary endpoints will be tested at an alpha level of 0.05 using the Holmes procedure.

CCI [redacted]

Analyses are based on the efficacy analysis set.

9.3.4 Adjustment for Multiplicity

Multiplicity is addressed in this study using a gatekeeping procedure (see Section 9.3.3).

9.3.5 Missing Data

Since this study is expected to be conducted in a hospital setting, we expect little or no missing data for the primary endpoint. Every effort will be made to contact subjects that are released from the hospital before Day 15 by telephone and determine their status for the primary endpoint. The statistical model for the primary endpoint will include all subjects, and is valid under the assumption of Missing At Random (MAR). Sensitivity analyses will assess the model under other assumptions regarding missingness.

9.3.6 Analysis of Safety

The investigators determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available. AEs are presented by system organ class and preferred term in descending order of overall frequency of events. If a subject had an AE with different intensities over time, then only the greatest intensity is reported.

Deaths, all AEs, and SAEs are listed for the enrolled analysis set.

The frequencies of the following safety events on study are summarized by treatment group and overall for the safety analysis set: SAEs; AEs by intensity and overall; treatment-emergent AEs by intensity and overall; AEs leading to study drug discontinuation; and treatment-emergent AEs by relationship to study drug.

Clinically significant laboratory test abnormalities on study will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in 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 Adverse Events Corrected Version 2.1 (2017). If a subject has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported.

Further safety analyses will be described in the SAP.

9.3.7 Futility Analysis

A formal futility analysis will be performed by the DMC statistician after approximately 50% of subjects complete the 14-day treatment period.

The DMC will test for futility stopping only. This test will not be counted against the alpha spend for the study. In particular, zavegepant will be tested for inferiority to placebo, on the primary endpoint (the six point, ordinal, severity scale). This will be done using a Wilcoxon rank sum test at a one-sided alpha level of 0.05.

9.4 Schedule of Analyses

A futility analysis will be conducted by the DMC statistician after approximately half of the subjects have reached Day 15.

The first planned analysis for this study may be executed after the last subject has reached Day 29 of the study, and the database has been locked. The last planned analysis will occur after the last subject has completed the Day 60 safety follow up.

Additional unplanned analyses may be executed as needed to protect subject safety and as requested by regulatory agencies.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), International Conference on Harmonization (ICH) guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any Independent Ethics Committee (IEC) requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

This study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion prior to initiation of the study.

All serious breaches must be reported to Biohaven (or designee) immediately. A Serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

The Principal investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the Informed Consent Forms (ICFs) to regulatory authorities when necessary.

10.2 Data Monitoring Committee (DMC)

An independent DMC will be utilized for this study. The DMC will review the safety of all subjects enrolled in trials on a regular basis.

The DMC will review the protocol and will identify the data parameters and format of the information to be regularly reported. The DMC will meet in person or by conference call according to the schedule specified in the DMC charter. The DMC will typically receive reports with data by treatment group (e.g. blinded group A, group B etc.) or, if requested by the DMC, completely unblinded.

Based on the review of safety data, the DMC will make recommendations regarding the conduct of the study to the clinical team. These may include continuing the study as designed, amending safety monitoring procedures, modifying the protocol or the informed consent form, or recommending the termination of the study. In addition, the DMC statistician will conduct a futility analysis using the primary endpoint, after approximately half of the subjects have reached Day 15.

For purposes of the DMC, data analysis will be carried out by the unblinded safety biostatistics team independent and firewalled from the team directly involved with the study design and primary analyses, and a report will be prepared for the DMC.

For further details please refer to the DMC charter.

10.3 Steering Committee

Not Applicable.

10.4 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IRB/IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), IB (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IRB/IEC favorable written approvals for the above-mentioned study documents.

In the event that the protocol is amended, the revised protocol must be approved by the IRB/IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial.

10.5 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Biohaven (or designee) will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, when possible, the subject must read, sign and date an IRB/IEC approved written informed consent form for study. The signed and dated ICF will be retained at the Investigator's site, with a copy provided to the study subject and date will be entered in his or her eCRF or appropriate system. Because this study involves

hospitalized subjects with an infectious disease, alternative consenting procedures as described in recent FDA guidance[52] may be used when necessary.

The IRB/IEC must review and approve all protocol versions and informed consent form versions and a copy of each version of the IRB/IEC approved protocol and informed consent form is to be retained in the Study Master file. Any revisions to the protocol or ICF will be reviewed and approved by the IRB/IEC and subjects will be informed of ICF changes and document continuing consent by signing and dating the revised version of the ICF.

If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IRB/IEC, prior to subsequently obtaining each subject's consent.

If informed consent is initially given by a subject's legal guardian or legally acceptable representative, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then the consent must additionally be obtained from the subject.

The informed consent form must also include a statement that Biohaven and its representatives and regulatory authorities may have direct access to subject records.

10.6 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation of each study subject. Data reported on the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Electronic CRFs will be prepared for all data collection fields when EDC is being used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator must retain a copy of the eCRFs including records of changes and corrections. If EDC is being used, signatures will be obtained electronically and a copy of the electronic eCRFs will be provided (or the data from the eCRFs) for future reference.

11 RECORDS MANAGEMENT

In accordance with the principles of GCP and GLP, the study may be inspected by regulatory authorities, the Sponsor and CRO. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

The investigator must retain all study records and source documents for the maximum time period required by the applicable regulations and guidelines, or institution procedures or for the period of time specified by the sponsor, whichever is longer. The investigator must contact the Sponsor prior to destroying any records associated with this study.

Biohaven will notify the investigators when the study files for this study are no longer needed.

If the investigator withdraws from the study (i.e., retirement, relocation), the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to Biohaven.

It is the responsibility of the investigator to ensure that the current disposition record of investigational product (may be supplied by the sponsor) is maintained at each study site where the study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

11.1 Source Documentation

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent for all subjects on study.

If source documents are created to support the collection of study information, this must be retained with the other pertinent medical records for each subject for verification of data points, unless otherwise instructed by the Sponsor or designee to enter data directly on the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

11.2 Study Files and Record Retention

The Sponsor does not require original documents that have already been scanned and entered into the electronic Trial Master File (eTMF) system to be forwarded to the Sponsor. Any original documents (i.e. 1572, signed financial disclosure, signed ICF, etc.) will be retained in the regulatory binder at the study site. The CRO will conduct a final eTMF reconciliation to ensure all study files and regulatory documents have been correctly uploaded to the eTMF prior to the close or termination of the study. Any materials or documents to support the clinical trial outside of the eTMF (i.e. rater training tapes) should be maintained by the CRO. The Sponsor will be contacted to determine whether the study documents/materials that are retained outside of the eTMF will be forwarded to the Sponsor, destroyed or kept at the CRO or at another facility for a longer period of time at the Sponsor's expense.

The CRO will maintain adequate study records after completion or termination of study. After that period, the Sponsor will be contacted to determine whether the study records will be forwarded to the Sponsor, destroyed or kept at CRO or at another facility for a longer period of time at the Sponsor's expense.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Biohaven (or specified designee). A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Biohaven or specified designee will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Biohaven, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

13 STUDY REPORT AND PUBLICATIONS

Biohaven (or specified designee) is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of Biohaven is discussed in the investigator's Clinical Research Agreement.

14 STUDY DISCONTINUATION

Both Biohaven and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Biohaven or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Biohaven and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Biohaven. However, authorized regulatory officials, IRB/IEC personnel, Biohaven and its authorized representatives are allowed full access to the records.

Identification of subjects and eCRFs shall be by initials (when allowed), screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

The Sponsor may approve the sharing of de-identified data from this study to be made available to researchers for the purpose of advancing the understanding the pathogenesis of COVID-19 disease or trial methodology. In any publication of this data, confidentiality of individual subjects will be protected.

16 CLINICAL PROTOCOL APPROVAL FORM

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

Study No: BHV3500-203

Original Protocol Date: 13 April 2020

Protocol Version No: V 7.0

Protocol Version Date: 11 May 2022

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Signature Approval	Date
Author: PPD , Clinical Operations	PPD	PPD
Clinical Operations: PPD , Clinical Operations	PPD	PPD
Biometrics: PPD Biostatistics	PPD PPD D	PPD , Ph.D. PPD
Medical Lead: PPD , MD PPD	PPD Digitally signed by PPD PPD	
Regulatory Affairs: PPD Regulatory Affairs	PPD Digitally signed by PPD Reason: I am approving this document PPD	PPD

17 APPENDICES

17.1 APPENDIX I – Names of Study Personnel

Sponsor:	Biohaven Pharmaceuticals Refer to contact list in study binder for contact information
Medical Monitor:	PPD, MD PPD PPD
Clinical Research Organizations:	Cognitive Research Corporation Refer to contact list in study binder for contact information
Pharmacovigilance:	PPD Refer to SAE, Pregnancy Surveillance Forms and study binder for contact information.

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