CLINICAL STUDY PROTOCOL

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

Protocol Number: BHV-3500-204

Name of Investigational Product:	Oral zavegepant
Phase of Development:	1b
Indication:	Allergic asthma
Contract Research Organization:	**Sponsor:**
Syneos Health, LLC 1030 Sync Street Morrisville, North Carolina 27560 USA Tel.: +1-919-876-9300	Biohaven Pharmaceuticals, Inc. 215 Church Street New Haven, CT 06510 USA Tel.: +1-203-404-0410
Protocol Version:	2.0
Protocol Date:	09 June 2021

PROTOCOL APPROVAL SIGNATURES

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

Protocol Number: BHV-3500-204

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

PPD

PPD

Signature

Date

Sponsor Signatory

PPD

PPD Clinical Operations

PPD

Signature

Date

Sponsor Signatory

PPD

Sr. Clinical Trial Lead

PPD

Date

Sponsor Signatory

PPD

PPD Biostatistics

PPD

Date

SUMMARY OF CHANGES

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	25 Mar 2021
Version 2.0	Sponsor Signatory section was updated to reflect recent staffing updates Updated section 5.2.1.5 to include more recent data Updated section 5.4.1 to clarify dose selection rationale Updated section 8.1, Inclusion criteria 3a to include an upper age limit of 65 years of age. The Synopsis was also updated to reflect this change Updated section 8.3 to clarify cervical cap with spermicidal gel Corrected inconsistencies and typographical errors throughout the protocol.	09 Jun 2021

INVESTIGATOR SIGNATURE PAGE

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Biohaven Pharmaceuticals, Inc. including but not limited to the current Investigator's Brochure.
- Once the protocol has been approved by the institutional review board (IRB)/research ethics board (REB)/independent ethics committee (IEC), I will not modify this protocol without obtaining prior approval of Biohaven Pharmaceuticals, Inc. and of the IRB/REB/IEC. I will submit the protocol amendments and/or any informed consent form modifications to Biohaven Pharmaceuticals, Inc. and the IRB/REB/IEC, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Biohaven Pharmaceuticals, Inc. study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third-party.
- Information developed in this clinical study may be disclosed by Biohaven Pharmaceuticals, Inc. to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Signature Date

_____

(Printed name)

_____

(Institution name)

2 SYNOPSIS

Title of Study:	A Phase 1b, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate Safety and Efficacy of Oral Zavegepant in Subjects With Mild Allergic Asthma
Protocol Number:	BHV-3500-204
Investigators/ Study Sites:	Approximately 6 sites
Phase of Development:	1b
Objectives:	The primary objective: • To evaluate the allergen-induced late asthmatic response (LAR) between subjects treated with zavegepant and placebo after 28 days of treatment. Secondary objectives: • To evaluate the allergen-induced early asthmatic response (EAR) between subjects treated with zavegepant and placebo. • To evaluate the allergen-induced airway hyperresponsiveness (AHR) measured at 24 hours post-allergen, between subjects treated with zavegepant and placebo. • To assess the safety and tolerability of oral zavegepant. CCI [redacted]
Study Endpoints:	Primary endpoint: • Allergen-induced LAR assessed as maximum percentage decrease in forced expiratory volume in 1 second (FEV_1) between 3 and 7 hours after the administration of the allergen inhalation challenge.

	CCI • [redacted] • [redacted] • [redacted] CCI CCI [redacted]
Study Design:	This study is designed as a double-blind, parallel-group, randomized study of 24 subjects to evaluate the safety and efficacy of 150 mg oral zavegepant (N=12) versus placebo (N=12) twice daily (BID) for the treatment of allergen-induced asthma. Individuals with stable, mild allergic asthma, with a history of episodic wheeze and shortness of breath, will be eligible for enrollment. The study will be divided into 2 parts. **Part 1 (screening period)**: A screening period of up to 28 days will be conducted to obtain a cohort of subjects with documented EAR (defined as $\geq$ 20% fall in FEV_1 0 to 2 hours after allergen challenge) and LAR (defined as $\geq$ 15% fall in FEV_1 3 to 7 hours after allergen challenge) to an inhaled incremental allergen challenge and AHR defined by methacholine PC_{20} $\leq$ 16 mg/mL by inhaled incremental methacholine challenge. Procedures for allergen and methacholine challenges are specifically outlined in section below—Efficacy/Clinical Performance/Effectiveness.
	At Visit 1, subjects will be confirmed for allergy by a skin prick test and assessed for safety by baseline clinical laboratory tests. Upon confirmation from blood tests that it is safe to proceed in Part 1, the subject will be scheduled for the screening allergen challenge triad which will occur over 3 consecutive days at Visits 2, 3, and 4.

	At Visit 2 (Day -15), allergen skin titration (only if procedure was not previously performed at Visit 1), methacholine challenge, and sputum induction will be performed. At Visit 3 (Day -14), allergen challenge and sputum induction will be performed. At Visit 4 (Day -13), methacholine challenge and sputum induction will be performed. A rest/washout period of 2 to 4 weeks is scheduled to allow recovery from the allergen challenge. If more than 4 weeks is required, Sponsor Medical Monitor should be consulted. **Part 2 (Dosing Period)**: Duration of study treatment in Part 2 will be approximately 28 days. At Visit 5 (predose) Day 1, a methacholine challenge will be performed. To continue to randomization, the subject's baseline lung function (FEV_1) and airway responsiveness to methacholine must show evidence of recovery to within 90% of baseline for FEV_1 and not more than 1 doubling dose below Visit 2 baseline for methacholine PC_{20}. If these criteria are met, sputum will be induced. If subjects have not recovered from the screening allergen challenge, additional time will be allowed, and Visit 5 pre-dosing procedures may be repeated. If this additional retest is required, the screening period may be extended. Subjects will then be randomized in a 1:1 ratio to receive 150 mg zavegepant or matching placebo to be taken BID. Subjects will take their first dose of zavegepant on a fasted stomach upon waking, and their second dose in the evening. Subjects should not consume food other than water for 1 hour after dosing. Further details in Section 9.3. All subjects will be scheduled for their 3-day allergen challenge triad (Visit 6/~Day 26, Visit 7/~Day 27, and Visit 8/~Day 28). Morning doses will be taken before any laboratory procedures, and study treatment will end with their evening dose at Visit 8 (~Day 28). A follow-up period consisting of an onsite visit (Visit 9) will be conducted approximately 7 to 10 days after the last study treatment.
Selection of Subjects:	Inclusion Criteria: 1. Subject must have mild intermittent asthma as defined by < 2 bronchodilator usage for treatment of asthma symptoms per week. 2. Baseline FEV_1 of $\geq$ 70% of predicted value. 3. Age and reproductive status: a) Male and female subjects aged $\geq$18 and $\leq$65 years.

	b) All subjects must understand the contraception requirements for this study and agree to use 2 acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 8.3 for the definition of women of childbearing potential (WOCBP). c) Women must not be pregnant, lactating or breastfeeding. d) At the baseline Visit 5, prior to dispensing study drug, WOCBP must have a negative urine pregnancy test. 4. Subject's score on the Sheehan-Suicidality Tracking Scale (S-STS) at screening must be 0. 5. Able to understand and give written informed consent and has signed a written informed consent form approved by the investigator's IRB/REB. 6. Able to understand and complete study-related questionnaires. 7. Willing and able to comply with study site visits and study-related procedures. The following inclusion criteria must be met for entry into the Dosing Phase (Part 2): 8. Positive methacholine challenge ($PC_{20} \leq 16$ mg/mL). 9. Positive skin prick test to common aeroallergens (including but not limited to cat, dust mite, grass, pollen). 10. Positive allergen-induced early and late airway bronchoconstriction. Exclusion Criteria: 1. Worsening of asthma or respiratory tract infection within 6 weeks prior to study entry. 2. Participation in any other investigational drug treatment protocol within the preceding 30 days or 5 half-lives, whichever is longer, of an investigational drug product. 3. Lung disease other than mild allergic asthma. 4. Body mass index (BMI) ≥ 33.0 kg/m^2. 5. Subjects who anticipate major changes in allergen exposure in their home or work environments that are expected to coincide with the baseline or the final assessments as assessed by the investigator. 6. History of liver disease. 7. History of HIV, hepatitis B or hepatitis C. 8. Use of tobacco products and/or vaping products within the previous 12 months or smoking history > 10 pack years. 9. Subjects should be excluded if they have a positive drug screen for drugs of abuse that, in the investigator's judgment, is medically significant and would impact the safety of the subject or the interpretation of the study results. In addition: a) Detectable levels of amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, phencyclidine (PCP), or

	methadone. Retesting for positive results that are exclusionary is not allowed. b) Detectable levels of marijuana in the drug screen are not exclusionary if, in the investigator's documented opinion, the subject does not meet Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for substance use disorder and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results. 10. Subject has a concomitant disease or condition that could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study, including, but not limited to, cancer, alcoholism, drug dependency or abuse, or psychiatric illness. 11. History of alcohol dependency within the past 12 months, as determined by investigator, is exclusionary. 12. Use of any exclusionary, prohibited, or restricted medications (including restricted asthma medications) as outlined in Section 9.6. 13. Use of any drugs known to induce or inhibit hepatic drug metabolism, including St. John's wort, within 30 days prior to the first dose of study drug. 14. History of anaphylaxis to any substance or a clinically important reaction to any drug. 15. Subject history with current evidence of uncontrolled, unstable, or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. 16. History of myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack in the 6 months (24 weeks) prior to screening. 17. History of uncontrolled hypertension or uncontrolled diabetes; however, subjects can be included who have stable hypertension and/or diabetes for 3 months (12 weeks) prior to screening; blood pressure > 140 mmHg systolic or 90 mmHg diastolic after 10 minutes of rest is exclusionary. 18. History of gastric or small intestinal surgery (including gastric bypass, gastric banding, gastric sleeve, gastric balloon, etc.), or has a disease that causes malabsorption. 19. History or diagnosis of Gilbert syndrome or any other active hepatic or biliary disorder. 20. History of gallstones or cholecystectomy. 21. Subject has hematologic or solid malignancy diagnosis within 5 years prior to screening. Subjects with a history of localized basal cell or squamous cell skin cancer are eligible for the study if they are cancer-free prior to the screening visit in this study. 22. Any of the following laboratory test values above the upper limit of normal (ULN) at the screening visit: aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin, indirect bilirubin, and total bilirubin. Only abnormal values between 1 and 1.5 × ULN may be repeated once for confirmation to below ULN.

	23. Any of the following abnormal laboratory test values at the screening visit: a) Hemoglobin < 12.0 g/dL for males and < 11.0 g/dL for females b) Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 mL/min/1.73m^2. c) Total white blood cell (WBC) count < 3.0 K/µL. d) Platelet count < 100 K/µL. e) Neutrophils < 1000/µL. f) Creatine phosphokinase (CPK) > 5 × ULN. 24. Any of the following abnormalities on 12-lead electrocardiogram (ECG) Visit 1: a) Left bundle branch block. b) Right bundle branch block with a QRS duration ≥ 150 msec. c) Intraventricular conduction defect with a QRS duration ≥ 150 msec. d) QTcF ≥ 470 msec (Fridericia's corrected QT interval). 25. Sex and reproductive status a) Females of childbearing potential who are unwilling or unable to use acceptable contraceptive methods or abstinence to avoid pregnancy for the entire study period and for 90 days after the study. See Section 8.3 for acceptable contraceptive methods. b) Women who are pregnant, lactating, or breastfeeding. c) Women with a positive pregnancy test. 26. History of a psychiatric disorder which, in the opinion of the investigator, would pose a safety risk to the subject or affect the subject's participation in the trial. 27. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the first dose of study drug, administration of a biological product in the context of a clinical research study within 5 half-lives prior to the first dose of study drug, or concomitant participation in an investigational study involving drug or device administration. 28. Any reason which, in the opinion of the investigator, would prevent the subject from participating in the study.
Planned Sample Size:	24 randomized subjects are planned in this study.
Investigational Therapy:	Oral zavegepant soft gelatin capsules, 150 mg twice daily (BID).
Reference Therapy:	Matching placebo soft gelatin capsules, 150 mg twice daily (BID).
Treatment Duration:	Approximately 28 days.
Efficacy/	**Methacholine Inhalation Tests.** See Section 11.1.1 for details.

Clinical Performance/ Effectiveness	**Allergen Inhalation Challenge.** See Section 11.1.2 for details. **Sputum Induction.** See Section 11.1.3 for details. **Skin Testing.** See Section 11.1.4 for details. **Allergen Skin Titration.** See Section 11.1.5 for details.
Safety:	After signing an informed consent, adverse events (AEs) encountered during the duration of the study will be recorded on the appropriate pages of the electronic case report form (eCRF). Unchanged, chronic conditions, or those related to the underlying disease or medical conditions that are consistent with natural disease progression, are not considered AEs and should not be recorded on AE pages of the eCRF unless there is an exacerbation of a chronic condition. AEs should be graded as follows: unrelated, unlikely related, possibly related, and related to study drug.
Pharmacokinetics:	A blood sample for pharmacokinetic (PK) measurement will be obtained predose (prior to the morning dose of study drug) on Visits 6, 7, and 8. Additional PK samples will be collected on Visit 7 at approximately 1 (+ 0.5 h) hour and 3 (+/- 0.5 h) hours postdose. Subjects should be instructed to hold their daily dose of study drug on the morning of Visits 6, 7, and 8 and arrive at the clinic after an overnight fast. Exact times of dosing and PK sample collection will be documented.
Other Assessments:	CCI 
Statistical Methods and Planned Analyses:	The early and late asthmatic response endpoints will be compared between zavegepant and placebo using analysis of covariance (ANCOVA) with respective baseline EAR and LAR data as covariate. Point estimates, 95% confidence intervals (CIs) and 2-sided p-value, will be reported for the treatment difference between zavegepant and placebo. Graphical summaries of the data from inhaled allergen challenges will be presented. Descriptive statistics will be provided for demographic, baseline characteristics, safety, PK, and biomarker data. Descriptive statistics on continuous variables will include number of subjects (N), mean, median,

	minimum, standard deviation, and ranges. Categorical data will be summarized using frequency counts and percentages. The number and percentage of subjects reporting any TEAE will be tabulated by system organ class and preferred term. Similar summaries will be provided for treatment-related AEs, serious AEs (SAEs), and AEs leading to treatment discontinuation. Clinically significant laboratory test abnormalities will be identified as Grade 3 to 4 laboratory test results.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AHR	airway hyperresponsiveness
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve 0 to 24 hours
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CIC	Clinical Investigator Collaborative
C_{max}	maximum concentration of drug
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
EAR	early asthmatic response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GM	geometric mean
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IN	intranasal
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-based response system
LAR	late asthmatic response
MAD	multiple ascending dose
ODT	orally disintegrating tablet
PBS	phosphate buffered saline
PC_{20}	provocation concentration causing a 20% decline in forced expiratory volume in 1 second (FEV_1)
P-gp	P-glycoprotein
PK	pharmacokinetic
PNEC	pulmonary neuroendocrine cells
PPD	Pharmaceutical Product Development
QD	once daily
REB	research ethics board
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SGC	soft gelatin capsule
SOP	standard operating procedure
S-STS	Sheehan-Suicidality Tracking Scale
TEAE	treatment-emergent adverse event
TRP	transient receptor potential
ULN	upper limit of normal
WOCBP	women of childbearing potential

5 INTRODUCTION

5.1 Background on Allergic Asthma

Asthma is a chronic inflammatory disease with the defining feature of airway hyperresponsiveness (AHR). There are many causes of asthma, leading to multiple endotypes, with allergic or atopic asthma being the most common. Allergic asthma is an antigen-specific, T cell mediated disease that leads to increased bronchoconstriction, eosinophil infiltration, and cytokine release, which amplifies and perpetuates the response. Shortly after allergen inhalation, patients with allergic asthma experience airway obstruction leading to an early asthmatic response (EAR), which results in a ≥ 20% drop in forced expiratory volume in 1 second (FEV_1) within 1 to 2 hours. Roughly 50% of these patients will experience a second bronchoconstriction event that is driven by inflammation during the 3 to 7 hours after exposure, leading to a drop in FEV_1 of ≥ 15% known as the late asthmatic response (LAR). The LAR may last for hours to days, is less amenable to bronchodilator therapy, and contributes to the chronic pathophysiologic changes of asthma that affect patient quality of life.

The neuroimmune axis plays several important roles in asthma, including AHR, antigen-sensing, immune response amplification, and in mediating the cough associated with asthma. Calcitonin gene-related peptide (CGRP) is a neuropeptide that plays a critical role in neuroimmune communication and has been shown in the literature to play a key role mediating the neuroimmune impacts on T cells, innate-immune cells, bronchoconstriction, and vasodilation. There are 2 primary sources of CGRP in the lung: transient receptor potential (TRP)-containing neurons and pulmonary neuroendocrine cells (PNECs). CGRP is a major component of vesicles within TRP-containing neurons, and animal models have suggested that these vesicles induce smooth muscle contraction in the airways (Tränkner et al 2014; Kim et al 2020; Springer et al 2004). PNECs are located at branch-junction points in both the human and mouse lung in close proximity to innate lymphoid cells which are implicated as key mediators of allergic asthma. When PNECs encounter inhaled antigens, they release CGRP to directly activate type 2 innate lymphoid cells (ILC2s) and amplify their production of type 2 inflammatory cytokine responses such as IL-5 and IL-13 (Sui et al 2018).

Lung samples from asthmatic patients show increased numbers of PNECs and increased CGRP reactivity, and asthmatic patients have elevated levels of CGRP in bronchial alveolar lavage fluid during the LAR (Sui et al 2018; Kay et al 2007). Furthermore, CGRP has been shown to bias CD4 + T cell polarization in animal models of inflammation, leading to amplified Th9 and Th17 responses (Ding et al 2016; Mikami et al 2012). Taken together, these data indicate a potential pathogenic role of aberrant CGRP signaling in asthmatic patients by causing AHR, amplifying innate-immune responses to allergen, and polarizing CD4 + T cell responses toward an asthmatic T2 phenotype.

Both asthma and migraine can be viewed as chronic inflammatory diseases characterized by recurrent flares ("migraine attack", "acute bronchoconstriction") due to triggers (e.g., environmental allergens or dietary triggers) that stimulate an aberrant biological response due to an underlying hyperresponsive neuroimmune system. In fact, there is a significant overlap of migraine and asthma patients, with migraine patients also having an increased risk of asthma (Buse et al 2020).

CGRP signaling impacts neurons, immune cells, and smooth muscle cells, and the CGRP receptor is located in central and peripheral nerves, smooth muscle cells, lymphocytes, dendritic cells, and macrophages. Zavegepant is a selective, competitive CGRP receptor antagonist being developed for the treatment of migraine. Zavegepant is being developed for intranasal (IN), oral soft gelatin capsule (SGC) and sublingual administration. Migraine, similar to asthma, is a chronic neuroinflammatory condition characterized by recurrent attacks triggered by external or internal stimuli with an underlying hyperresponsive state. CGRP receptor antagonism has been demonstrated to be safe and effective for both acute and preventive treatment of migraine. When used as an acute treatment for migraine attacks, CGRP receptor antagonists have been shown to reduce the frequency of subsequent attacks. This suggests that treatment of acute attacks decreases the hyperresponsiveness of the underlying disease state.

The aim of this study is to test the hypothesis that CGRP receptor antagonism will mitigate the LAR and airway hyperresponsiveness by reducing excessive CGRP in allergic asthma. The study will use the third-generation small molecule CGRP receptor antagonist zavegepant.

5.2 Background on Zavegepant

CCI [redacted]

[redacted]

See Section 9.1 for further investigational product (IP) details; see also Sponsor's zavegepant (BHV-3500) Investigator's Brochure (IB) version 4.0 for IP SGC composition details.

5.2.1 Clinical Experience

A summary of the nonclinical and clinical investigational programs can be found in Sponsor's current zavegepant BHV-3500 IB.

CCI [redacted]

CCI

[redacted]

5.2.1.3 Phase 2/3 Dose-Ranging Study BHV3500-201

The pivotal Phase 2/3 dose-ranging study evaluating the safety and efficacy of 3 different IN dose levels (5 mg, 10 mg, 20 mg) of zavegepant, relative to placebo, in the acute treatment of migraine with moderate to severe pain intensity has concluded. Preliminary data from

BHV3500-201 indicate that zavegepant as a single IN spray containing 5 mg, 10 mg, or 20 mg was well tolerated in adult subjects with moderate to severe migraine attacks and demonstrated a favorable safety profile compared with placebo. The study met the primary endpoint, and the 10 mg dose was identified as the lowest efficacious dose demonstrating statistically significant efficacy.

No deaths were reported in the study. SAEs were reported in 2 subjects on treatment including: thrombosis reported in 1 subject from the 10 mg group; and vestibular migraine reported in 1 subject in the placebo group. Both events were moderate in intensity and judged by the investigator as not related to study therapy. The SAE of thrombosis was reported 13 days after the single dose of zavegepant as post-trauma from an automobile accident. Additional details are provided in the current BHV-3500 IB.

CCI [redacted]

[redacted]

5.3 Clinical Risks/Benefits of Zavegepant

There are no changes in the overall risk benefit profile of zavegepant relative to version 4.0 of the IB. CCI [redacted] Administration of zavegepant as a single IN 5 mg, 10 mg, and 20 mg spray was well tolerated in adult subjects with moderate to severe migraine and demonstrated a favorable safety profile CCI [redacted]. Ongoing evaluation of blinded data in trials for oral zavegepant (BHV3500-103, BHV3500-107) suggest that the drug is well tolerated. The overall risk benefit profile remains unchanged.

5.3.1 Risks Associated With SARS-CoV-2

Certain provisions may be implemented to minimize potential hazards to study participants due to coronavirus disease 2019 (COVID-19). These provisions may allow adjustments to visit intervals; however, prior discussion and approval by Sponsor is required.

Investigators should be alerted to the development of COVID-19 and consider whether or not participation is in the subject's best interest to continue participation in the trial. Investigators should consider early termination for subjects that develop COVID-19 confirmed or presumed infection during the screening period or before Visit 5.

5.4 Study Rationale

Biohaven Pharmaceuticals, Inc. is developing multiple formulations of zavegepant for treatment and prevention of migraines, including a new oral SGC of zavegepant (BHV-3500) for the treatment of migraine. Asthma, like migraine, can be viewed as a chronic inflammatory disease characterized by recurrent flares ("migraine attack", "acute bronchoconstriction") due to triggers (e.g., environmental allergens or dietary triggers) that stimulate an aberrant biological response due to an underlying hyperresponsive neuroimmune system. When used as an acute treatment for migraine attacks, CGRP receptor antagonists have been shown to reduce the frequency of subsequent attacks. This suggests that treatment of acute attacks decreases the hyperresponsiveness of the underlying disease state.

The aim of this study is to test the hypothesis that CGRP receptor antagonism will mitigate the LAR and airway hyperresponsiveness by reducing excessive CGRP in allergic asthma. The goal of this study is to assess the efficacy and safety of twice daily (BID) dosing of zavegepant at an oral dose that produces systemic exposures similar to or greater than those produced from daily exposures from the 10 mg clinical dose given intranasally to treat acute migraine. Overall, the goal is to begin to evaluate CGRP receptor antagonism for long-term treatment of asthma. This is done with Global Initiative for Asthma (GINA) goals for asthma medications at the forefront, which are: (1) to achieve and maintain control symptoms; (2) to maintain normal activity levels, including exercise; (3) to maintain pulmonary function as close to normal as possible; (4) to prevent asthma exacerbations; (5) to avoid adverse effects from asthma medications; and (6) to prevent asthma mortality.

Proof of concept will be demonstrated by measuring and comparing the LAR in zavegepant-treated versus placebo-treated mild allergic asthmatics who are exposed to allergen stimulus of their airways. This allergen-induced LAR will be evaluated after 28 days of BID dosing of 150 mg oral zavegepant (total daily dose 300 mg) through direct comparison of the maximum percentage decrease in FEV_1 between 3 and 7 hours after the allergen challenge in both groups.

5.4.1 Dose Selection Rationale

CCI [redacted]

CCI [redacted] In order to achieve s similar maximal inhibition of CGRP at peak concentration to that from a 10 mg IN dose (minimum effective dose for the acute treatment of migraine headache), and continuous inhibition of CGRP throughout a dosing interval, a 150 mg BID dosing regimen has been selected for the current study. CCI [redacted]

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

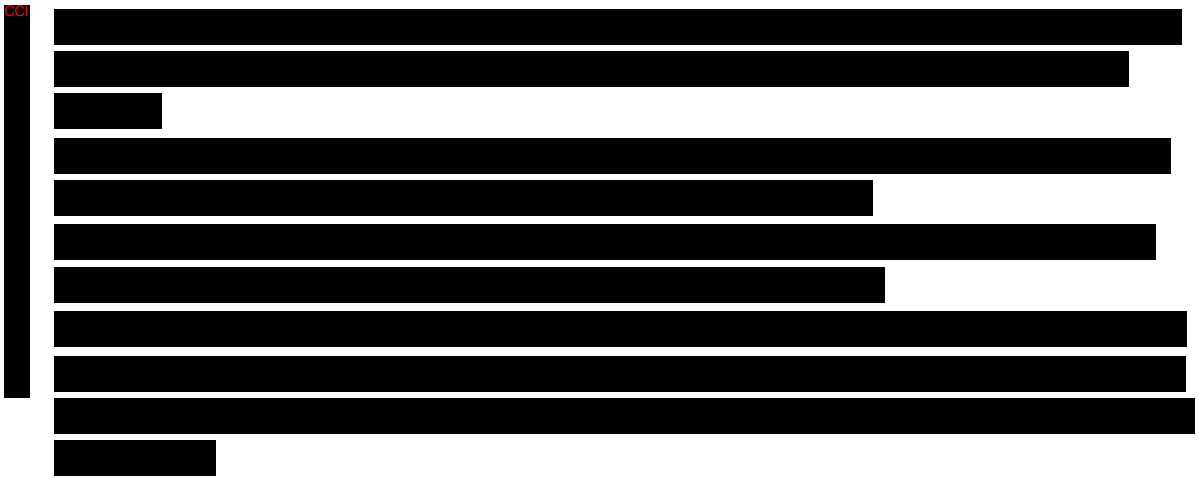
6.1.1 Primary Objective

- To evaluate the allergen-induced LAR between subjects treated with zavegepant and placebo after 28 days of treatment.

6.1.2 Secondary Objectives

- To evaluate the allergen-induced EAR between subjects treated with zavegepant and placebo.
- To evaluate the allergen-induced AHR measured at 24 hours post-allergen, between subjects treated with zavegepant and placebo.
- To assess the safety and tolerability of oral zavegepant.

CCI [redacted]



6.2 Study Endpoints

6.2.1 Primary Endpoint

- Allergen-induced LAR assessed as maximum percentage decrease in FEV_1 between 3 and 7 hours after the administration of the allergen inhalation challenge.

6.2.2 Secondary Endpoints

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

- Safety and tolerability of oral zavegepant assessed using the frequency of TEAEs and serious TEAEs through end of study, and clinically significant laboratory abnormalities.

CCI [redacted]

CCI [redacted]

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This Phase 1b study is designed as a double-blind, parallel-group, randomized study of 24 subjects to evaluate the safety and efficacy of 150 mg oral zavegepant (N=12) versus placebo (N=12) BID for the treatment of allergen-induced asthma. Individuals with stable, mild allergic asthma, with a history of episodic wheeze and shortness of breath, will be eligible for enrollment.

The study will be divided into 2 parts.

Part 1 (Screening period): A screening period of up to 28 days will be conducted to obtain a cohort of subjects with documented EAR (defined as ≥ 20% fall in FEV_1 0 to 2 hours after allergen challenge) and LAR (defined as ≥ 15% fall in FEV_1 3 to 7 hours after allergen challenge) to an inhaled incremental allergen challenge and AHR defined by methacholine PC_{20} ≤ 16 mg/mL by inhaled incremental methacholine challenge. Procedures for allergen and methacholine challenges are specifically outlined in Section 11.1.

At Visit 1, subjects will be confirmed for allergy by a skin prick test and assessed for safety by baseline clinical laboratory tests. Upon confirmation from blood tests that it is safe to proceed in Part 1, the subject will be scheduled for the screening allergen challenge triad which will occur over 3 consecutive days at Visits 2, 3, and 4.

At Visit 2 (Day -15), subjects will be confirmed for allergy by a skin prick (only if procedure was not previously performed at Visit 1). At approximately 24 hours before the allergen challenge, subjects will be assessed for AHR by methacholine challenge (methacholine PC_{20} must be ≤ 16 mg/mL), and a sputum sample will be induced.

At Visit 3 (Day -14), subjects will be challenged with an allergen for which they tested positive on skin prick testing. At approximately 7 hours post-allergen challenge, a sputum sample will be induced. Spirometry will be measured regularly until 7 hours post-allergen challenge and a sputum sample will be induced after the last spirometry measurement.

At Visit 4 (Day -13), at approximately 24 hours post-allergen challenge, methacholine challenge and sputum induction will be performed.

Washout period: A rest/washout period of 2 to 4 weeks to confirm subject lung function and airway responsiveness to methacholine has recovered (e.g., return of FEV_1 to within 90% of baseline and methacholine PC_{20} not more than 1 doubling dose lower than baseline). If more than 4 weeks is required, Sponsor Medical Monitor should be consulted.

Part 2 (Dosing period): Duration of study treatment in Part 2 will be approximately 28 days.

At Visit 5/Day 1 (predose), a methacholine challenge will be performed. To continue to randomization, the subject's baseline lung function (FEV_1) and airway responsiveness to methacholine must show evidence of recovery to within 90% of baseline for FEV_1 and not more

than 1 doubling dose below Visit 2 baseline for methacholine PC_{20}. If these criteria are met, sputum will be induced. If subjects have not recovered from the screening allergen challenge, additional time will be allowed, and Visit 5 pre-dosing procedures may repeated. If additional retest is required, the screening period may be extended beyond 4 weeks.

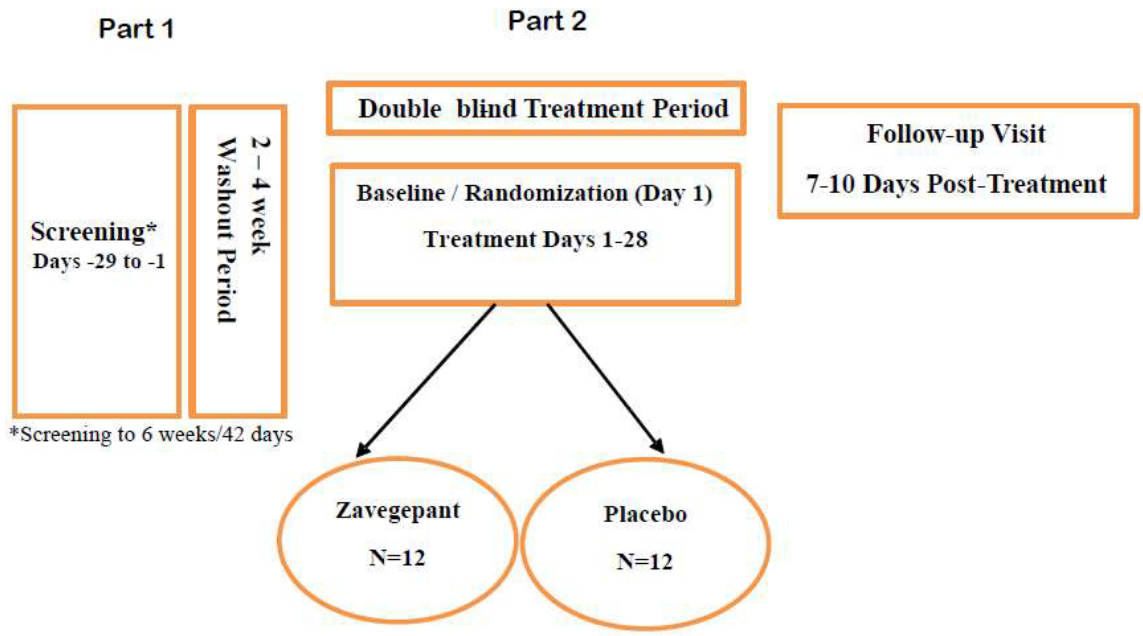
Subjects will then be randomized in a 1:1 ratio to receive 150 mg zavegepant or matching placebo to be taken BID. Subjects will take their first dose of zavegepant on a fasted stomach upon waking, and their second dose in the evening. Subjects should not consume food other than water for 1 hour after dosing.

All subjects will be scheduled for their 3-day allergen challenge triad (Visit 6/~Day 26, Visit 7/~Day 27, and Visit 8/~Day 28). Morning doses will be taken before any laboratory procedures. Study treatment will end with the subject's evening dose at Visit 8 (~Day 28). A follow-up period consisting of an onsite visit (Visit 9) will be conducted approximately 7 to 10 days after the last study treatment.

Additional dosing/fasting details are provided in Section 9.3.

Figure 1 presents the general study schematic.

Figure 1. Study Schematic



7.2 Discussion of Study Design

Neuroimmune interactions have been linked to several chronic and inflammatory conditions, including asthma. While a heterogeneous disease comprising many different endotypes, all types of asthma share the pathognomonic feature of AHR. While multiple animal models deficient in CGRP signaling demonstrate blunted or resistant responses to allergen challenge, to date there has been no clinical study of a CGRP signaling antagonist in asthmatics. Based on the body of evidence, a trial of a safe CGRP signaling antagonist is warranted in the asthmatic setting. Zavegepant is an oral CGRP receptor antagonist with a strong safety profile, currently being studied in Phase 3 trials for the treatment of migraine.

As CGRP is found in elevated concentrations in the sputum from those patients who experience an LAR event compared to non-responding patients, and there are observed changes in immune responses when CGRP is elevated toward an allergic asthmatic Th2/Th17 response, this study will focus on the allergic asthmatic population, and specifically the EAR and LAR to allergen.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including follow-up, as indicated in the Schedule of Assessments (Table 10-1).

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be enrolled and randomized in the study.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject must have mild intermittent asthma as defined by < 2 bronchodilator usage for treatment of asthma symptoms per week.
2. Baseline FEV_1 of ≥ 70% of predicted value.
3. Age and reproductive status:
   a) Male and female subjects aged ≥ 18 and ≤ 65 years.
   b) All subjects must understand the contraception requirements for this study and agree to use 2 acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 8.3 for the definition of women of childbearing potential (WOCBP).
   c) Women must not be pregnant, lactating or breastfeeding.
   d) At the baseline Visit 5, prior to dispensing study drug, WOCBP must have a negative urine pregnancy test.
4. Subject's score on the Sheehan-Suicidality Tracking Scale (S-STS) at screening must be 0.
5. Able to understand and give written informed consent and has signed a written informed consent form (ICF) approved by the investigator's Institutional Review Board (IRB)/research ethics board (REB).
6. Able to understand and complete study-related questionnaires.
7. Willing and able to comply with study site visits and study-related procedures.

The following inclusion criteria must be met for entry into the dosing phase (Part 2):

8. Positive methacholine challenge (PC_{20} ≤ 16 mg/mL).
9. Positive skin prick test to common aeroallergens (including but not limited to cat, dust mite, grass, pollen).
10. Positive allergen-induced early and late airway bronchoconstriction.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Worsening of asthma or respiratory tract infection within 6 weeks prior to study entry.
2. Participation in any other investigational drug treatment protocol within the preceding 30 days or 5 half-lives, whichever is longer, of an investigational drug product.
3. Lung disease other than mild allergic asthma.

4. Body mass index (BMI) $\geq$ 33.0 kg/m^2.
5. Subjects who anticipate major changes in allergen exposure in their home or work environments that are expected to coincide with the baseline or the final assessments as assessed by the investigator.
6. History of liver disease.
7. History of HIV, hepatitis B or hepatitis C.
8. Use of tobacco products and/or vaping products within the previous 12 months or smoking history > 10 pack years.
9. Subjects should be excluded if they have a positive drug screen for drugs of abuse that, in the investigator's judgment, is medically significant and would impact the safety of the subject or the interpretation of the study results. In addition:
    a) Detectable levels of amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, phencyclidine (PCP), or methadone. Retesting for positive results that are exclusionary is not allowed.
    b) Detectable levels of marijuana in the drug screen are not exclusionary if, in the investigator's documented opinion, the subject does not meet Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for substance use disorder and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results.
10. Subject has a concomitant disease or condition that could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study, including, but not limited to, cancer, alcoholism, drug dependency or abuse, or psychiatric illness.
11. History of alcohol dependency within the past 12 months, as determined by investigator, is exclusionary.
12. Use of any exclusionary, prohibited, or restricted medications (including restricted asthma medications) as outlined in Section 9.6.
13. Use of any drugs known to induce or inhibit hepatic drug metabolism, including St. John's wort, within 30 days prior to the first dose of study drug.
14. History of anaphylaxis to any substance or a clinically important reaction to any drug.
15. Subject history with current evidence of uncontrolled, unstable, or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia.
16. History of myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischemic attack in the 6 months (24 weeks) prior to screening.
17. History of uncontrolled hypertension or uncontrolled diabetes; however, subjects can be included who have stable hypertension and/or diabetes for 3 months (12 weeks) prior to

screening; blood pressure > 140 mmHg systolic or 90 mmHg diastolic after 10 minutes of rest is exclusionary.

18. History of gastric or small intestinal surgery (including gastric bypass, gastric banding, gastric sleeve, gastric balloon, etc.), or has a disease that causes malabsorption.
19. History or diagnosis of Gilbert syndrome or any other active hepatic or biliary disorder.
20. History of gallstones or cholecystectomy.
21. Subject has hematologic or solid malignancy diagnosis within 5 years prior to screening. Subjects with a history of localized basal cell or squamous cell skin cancer are eligible for the study if they are cancer-free prior to the screening visit in this study.
22. Any of the following laboratory test values above the upper limit of normal (ULN) at the screening visit: aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin, indirect bilirubin, and total bilirubin. Only abnormal values between 1 and 1.5 × ULN may be repeated once for confirmation to below ULN.
23. Any of the following abnormal laboratory test values at the screening visit:
    a) Hemoglobin < 12.0 g/dL for males and < 11.0 g/dL for females
    b) Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 mL/min/1.73m2.
    c) Total white blood cell (WBC) count < 3.0 K/µL.
    d) Platelet count < 100 K/µL.
    e) Neutrophils < 1000/µL.
    f) Creatine phosphokinase (CPK) > 5 × ULN.
24. Any of the following abnormalities on 12-lead ECG or blood pressure at screening Visit 1:
    a) Left bundle branch block.
    b) Right bundle branch block with a QRS duration ≥ 150 msec.
    c) Intraventricular conduction defect with a QRS duration ≥ 150 msec.
    d) QTcF ≥ 470 msec (Fridericia's corrected QT interval).
25. Sex and reproductive status
    a) Females of childbearing potential who are unwilling or unable to use acceptable contraceptive methods or abstinence to avoid pregnancy for the entire study period and for 90 days after the study. See Section 8.3 for acceptable contraceptive methods.
    b) Women who are pregnant, lactating, or breastfeeding.
    c) Women with a positive pregnancy test.
26. History of a psychiatric disorder which, in the opinion of the investigator, would pose a safety risk to the subject or affect the subject's participation in the trial.
27. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the first dose of study drug, administration of

a biological product in the context of a clinical research study within 5 half-lives prior to the first dose of study drug, or concomitant participation in an investigational study involving drug or device administration.

28. Any reason which, in the opinion of the investigator, would prevent the subject from participating in the study.

8.3 Contraception and Reproductive Potential

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal. Tubal ligation is considered one form of contraception; therefore, one additional form of contraception must be used to fulfill contraception requirements for the study. Essure®, tubal occlusion, and endometrial ablation are not acceptable methods of contraception. Menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL. **Note**: FSH level testing is not required for women ≥ 62 years of age with amenorrhea of ≥ 1 year

-OR-

- Woman on hormone replacement therapy who no longer menstruate. WOCBP and all men must understand the following requirements and use an acceptable method of contraception to avoid pregnancy throughout the study and for up to 90 days after the last dose of IP 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 in this study. Oral estrogen and progestin hormonal contraceptives as a sole method of contraception are therefore prohibited.

It is required that all WOCBP use 2 methods of contraception to prevent pregnancy, for the duration of the study (i.e., this study begins with signing the consent form through 90 days after dosing with study drug). The 2 methods should include 1 barrier method (e.g., condom with spermicidal gel, non-hormonal intrauterine devices, cervical cap with spermicidal gel) and 1 other method. The other method could include another barrier method or hormonal contraceptives (e.g., oral contraceptives, injectable contraceptives, patch, or contraceptive implant [e.g., hormonal intrauterine device]) started at least 4 weeks prior to sexual intercourse.

Males with partners who are WOCBP agree to use condoms with a spermicide during treatment and agree to encourage their partners to use one additional form of contraception for the duration of the study (i.e., this study begins with signing the consent form through 90 days after dosing with study drug). This additional form of contraception could be either a barrier method or a

hormonal contraceptive (e.g., hormonal or non-hormonal intrauterine devices, cervical cap with spermicidal gel, oral contraceptives, injectable contraceptives, patch, contraceptive implant).

Males with vasectomies are considered surgically sterile provided the procedure occurred greater than 6 months (24 weeks) prior to the screening visit. Vasectomy is considered one form of contraception; therefore, one additional form of contraception must be used to fulfill the contraception requirements for the study. Male subjects must not donate sperm until 90 days following the last dose of study drug.

Subjects who report abstinence, or who report exclusively being in same-sex relationships are still required to understand the contraception requirements in this study to prevent pregnancy. If subjects who report abstinence, or who report exclusively being in a same-sex relationship engage in heterosexual activity, then the contraception requirements must be followed.

All WOCBP must complete the pregnancy test schedule per Schedule of Assessments (Table 10-1). Women who suspect that they have become or may have become pregnant despite using proper birth control methods, should not take study drug and should immediately contact the investigator.

8.4 Screen Failures

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria will screen fail. There are some exceptions where retesting is permitted, as outlined in Section 8.5.

8.5 Retesting During the Screening Period

Retesting during the screening period does not require subject to reconsent for the trial.

Subjects who fail the baseline requirement of $FEV_1 \geq 70\%$ of predicted value or who do not meet the protocol requirements for AHR, EAR, or LAR, may be retested 1 time for each outcome.

8.6 Study Withdrawal, Removal, and Replacement of Subjects

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to withdraw consent from the study at any time and for whatever reason, without any prejudice. The Sponsor and the investigator or designee may discontinue study drug or withdraw any participant from the study for reasons described below:

- subject request (consent withdrawal);
- safety reasons;
- non-compliance with study drug or protocol requirements;
- significant protocol deviation;
- positive pregnancy test.

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be asked to complete the Visit 9 follow-up within 7 to 10 days of the last administration of study drug to complete assessments as indicated in the Schedule of Assessments (Table 10-1).

In the event that a subject discontinues prematurely from the study because of a TEAE or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator and medical monitor to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not reenter the study.

Participants who withdraw or are withdrawn from the study after dosing may be replaced at Sponsor's discretion.

As soon as participant withdrawal is confirmed, sampling and scheduling will be stopped. Study exit procedures will be performed at the time of withdrawal from the study or as soon as possible thereafter.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An investigator may choose to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

8.6.1 Lost to Follow-up

A subject 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 subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject 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 subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address). These contact attempts should be documented in the subject's study files.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

9 STUDY TREATMENT

9.1 Zavegepant Investigational Product

Zavegepant (BHV-3500), formerly BMS-742413 vazegepant, is a high-affinity (Ki = 0.023 nM) small molecule antagonist at the human CGRP receptor under development for the treatment of migraine. A full complement of pharmacology, safety pharmacology, PK, metabolism, and toxicology studies were conducted to assess the efficacy and safety of zavegepant; details are provided in Sponsor's IB.

9.1.1 Physical, Chemical, and Pharmaceutical Properties

Zavegepant SGC are manufactured by suspending the BHV-3500 hydrochloride in a mixture of medium chain triglycerides, glycerol monocaprylo caprate, polysorbate 80, colloidal silicone dioxide and D- and L-alpha tocopherol as excipients. Each SGC contains 25 mg of zavegepant (free base) for oral administration.

9.1.2 Study Drug Preparation

Not applicable.

9.1.3 Storage and Use

Zavegepant SGC capsules should be stored at 20 °C to 25 °C (68 °F to 77 °F) protected from light. Excursions to 15 °C to 30 °C are permitted.

9.1.4 Packaging and Labeling

All study drug supplies will be provided by the Sponsor (or third-party designee).

Zavegepant 25 mg SGC or matching placebo will be packaged in blister packs and will hold 48 capsules that are heat sealed into a wallet; 8 wallets will be placed into a subject specific carton/kit. The kits and wallets will have a unique identifier (kit/wallet number) included on the label. Each wallet will cover 4 days of AM (6 capsules) and PM (6 capsules) dosing. Please reference the Pharmacy Manual for additional details.

An interactive web-based response system (IWRS) system will be used to assign kits/wallets by a unique identifier to be dispensed to the subject.

The blister packs will not require labeling, but kits/wallets will have a full clinical label on the outside and will contain information required by local regulations.

9.2 Non-Investigational Product

Not applicable.

9.3 Dosage and Administration

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

9.3.1 Method of Study Treatment Assignment

After informed consent is obtained and study criteria is met at screening, the investigator or designee will obtain a subject number and treatment assignment via an IWRS. The IWRS system will assign a subject specific blinded study treatment kit that will contain 8 wallets, enough for the total treatment duration, to be dispensed to subjects. Once the kits/wallets have been assigned, they cannot be dispensed to another study subject. Sites will be responsible for recording the kit and wallet 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.

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

9.3.2 Blinding

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

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

9.4 Accountability and Compliance

The blinded pharmacist or other designated individual at the study site will maintain records of study treatment delivered, manage inventory at the site, distribution and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, lot/kit/wallet numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study subjects. 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.

At each visit after initiation of treatment, study site personnel will record compliance of the subject with the assigned regimen. The same study drug kits/wallets dispensed at Visit 5 will be used for study drug dosing through Visit 8. Subjects will be instructed to bring kits/wallets containing unused/partially used/empty wallets back for inspection at each study visit, or unscheduled site visit, if applicable. Subjects are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

Investigative site staff will maintain records that adequately document that the subjects were provided with the correct study treatment kits/wallets and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the Sponsor until accountability is completed at the end of the study and all wallets and IP documentation has been fully monitored.

Medication kits/wallets must be returned to the site at the end of the trial, as compliance will be assessed by capsule counts. Subjects have to be counseled on the importance of taking the study drug as directed. If poor compliance continues, (i.e., more than 1 missed dose in a week or cancellation of any site visit) discontinuation of the subject from the trial should be considered. If there are concerns about subject compliance, contact the clinical research organization (CRO)/Sponsor for guidance.

The morning dose of study drug treatment at Visits 5 through 8 will be supervised for compliance by study site personnel.

9.5 Dosage Modification

Dose modification is not allowed in this trial.

9.6 Prohibited and Concomitant Medications

All concomitant medication and therapy, including vaccines, used from 30 days before trial participation through end of study should be documented on the eCRF. This includes both prescription and non-prescription drugs.

The use of any CGRP receptor antagonist treatment or CGRP antibody is prohibited from 6 months prior to the screening until study completion/early termination.

Chronic use of any other medication for treatment of allergic lung disease other than short-acting ß2-agonists is prohibited.

See Table 9-1 and Table 9-2 for prohibited and restricted medications, respectively.

Table 9-1. Prohibited Medications

Prohibited medications	Restriction window/Washout
CGRP-targeting medications (prophylactic or acute)	6 months prior to Screening
Anti-IgE therapy Allergy immunotherapy	5 months before Screening 4 months before Screening
Investigational drug	30 days or 5 half-lives (whichever is longer) before Screening
Systemic corticosteroids Inhaled corticosteroids Topical nasal corticosteroids Immunosuppressives Anticoagulants Theophylline Nedocromil or cromoglycate Modafinil St. John's wort	28 days before Screening
Atypical antipsychotics such as aripiprazole, olanzapine, quetiapine, ziprasidone, or risperidone	12 months prior to Screening
Mood stabilizers such as lithium, lamotrigine or divalproex/valproic acid/valproate	12 months prior to Screening
Strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers (list below is not all-inclusive): Inhibitors: clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and	28 days or 5 half-lives (whichever is longer) before Screening If use of a strong CYP3A4 inhibitor or inducer is required during the trial, dosing should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inhibitor/inducer

Prohibited medications	Restriction window/Washout
ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole Inducers: apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort	
Potent P-glycoprotein (P-gp) inhibitors or inducers (list below is not all-inclusive): Inhibitors: amiodarone, clarithromycin, cyclosporine, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ritonavir, verapamil Inducers: carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	28 days or 5 half-lives (whichever is longer) before Screening If use of potent P-gp inhibitor or inducer is required during the trial, dosing should be stopped and should not start again until 14 days after the last dose of potent P-gp inhibitor/inducer
Leukotriene modifiers Long and moderate-acting beta-agonists Long-acting anticholinergics Antimuscarinics	14 days before Screening
Non-steroidal anti-inflammatory drugs	3 days before Screening

Sources: US FDA Table of Substrates, Inhibitors and Inducers; Hachad et al., 2010

Table 9-2. Restricted Medications

Restricted Medications	Restriction Window
Short-acting beta2 agonists Short-acting anticholinergics	8 hours before all study visits
Aspirin	7 days before allergen challenge and dosing
Short-acting antihistamines	3 days before allergen challenges
Intermediate-acting antihistamines	4 days before skin testing and allergen challenges
Long-acting antihistamines	9 days before skin testing and allergen challenges
Acetaminophen	Limited to no more than 1000 mg/day for a maximum of 2 consecutive days
Inhaled corticosteroids Systemic corticosteroids	If rescue treatment is required during the screening period, 1-week washout from acute dosing
Methlyxanthines	4 hours before spirometry
Long-acting beta-agonist Leukotriene modifiers	If rescue treatment is required during the screening period, 2-week washout from acute dosing
OTC drugs, including cold and allergy medications	72 hours prior to methacholine and allergen challenges

Lifestyle restrictions include:

- No alcohol within 48 hours prior to study visits.
- No strenuous exercise within 8 hours of study visits.
- No caffeine-containing products or medications for 12 hours prior to methacholine and allergen challenges.

10 STUDY PROCEDURES

Table 10-1 outlines the timing of procedures and assessments to be performed throughout the study. See Section 11 and Section 12 for additional details regarding efficacy assessments and safety assessments, respectively. Section 12.9 specifies laboratory assessment samples to be obtained.

Table 10-1. Schedule of Assessments

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

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

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

a **Part 1**: All screening procedures will be completed and results returned within Days -29 to Day -13.
b **Part 2/Day 1**: Subjects will be confirmed as recovered on Day 1 (e.g., confirmation of hyperresponsiveness recovery of methacholine PC_{20} not more than 1 doubling dose lower than baseline; return to FEV_1 within 90% of baseline) prior to initiation of dosing.
c A full examination will be performed at screening and at follow-up. BMI will be calculated at Screening Visit 1.
d Serum pregnancy test conducted at screening; urine pregnancy testing at all other visits as indicated. Results of the pregnancy test are required before dosing. Source documents should document that WOCBP agree to use 2 effective forms of contraception and men with WOCBP partners agree to use condoms with a spermicide during treatment.
e Allergen skin titration test can be performed at either Visit 1 or Visit 2 to allow for flexibility.
f After randomization, daily dosing in Part 2 from Visit 5 through Visit 8, inclusive. No onsite visit required after start of study medication at Visit 5 to start of allergen triad (Visit 6). Every effort should be made to conduct the study visits within the specified windows in Part 2. However, if necessary due to local COVID-19 safety requirements, visits may be performed outside of these windows in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance.

g Subjects should dose consistently at the same time of day, preferably in the morning and evening. Each dose of study drug should be taken while fasting (e.g., at least 1 h before breakfast/first meal of the day for the first dose, and at least 4 h after the previous meal for the second dose). Subjects should not consume food other than water for 1 h after dosing.
h Subjects will be asked to complete a daily diary to capture date and times of both meals and study drug administration.
i Pharmacokinetic sampling to be conducted predose on Visits 6, 7, and 8, and additionally at Visit 7 at approximately 1 (+ 0.5 h) h and 3 (+/- 0.5 h) h postdose. Subjects should be instructed to hold their daily dose of study drug on the morning of Visits 6, 7, and 8 and arrive at the clinic after an overnight fast. Exact times of dosing and PK sample collection will be documented.

10.1 Informed Consent

Before performing any study-related procedures, the investigator (or designee) will obtain a signed ICF from each subject. Further guidance requirements for ICFs are outlined in Section 16.1.3.

For rescreening of subjects, see Section 8.4 for informed consent requirements.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 10-1). If necessary due to local COVID-19 safety requirements, visits may be performed outside of these windows in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance.

Efficacy, clinical performance, and effectiveness assessments are described in Section 11 and include methacholine inhalation tests, allergen inhalation challenge, sputum induction, allergy skin test, and allergy skin titration.

Safety assessments are described in Section 12 and include AEs, physical examinations, vital signs, ECGs, and laboratory assessments.

10.2.1 Part 1 – Screening Period

The screening period includes screening procedures to determine initial eligibility (Visit 1) and methacholine and allergen challenge assessments (Visits 2, 3, and 4). The subject must undergo and pass all eligibility assessments in order to participate in the Part 2 dosing phase of the study.

Visit 1: Day -29 to Day -16 (onsite)

- Written informed consent will be obtained.
- Inclusion/exclusion will be assessed.
- Demographics, medical history, and medication history will be obtained and recorded.
- Concomitant and ongoing medications will be recorded.
- Vital signs will be measured (sitting blood pressure [systolic and diastolic blood pressure], heart rate, respiratory rate, body temperature).
- A physical examination will be performed, including BMI.
- A resting 12-lead ECG will be performed; subject should be in a resting, supine, or semi-recumbent position for at least 5 minutes.
- Spirometry measurements will be performed.
- WOCBP will undergo serum pregnancy testing. This pregnancy test must be negative in order for the subject to participate in the study and receive drug. WOCBP must await the results of the pregnancy test before receiving drug. WOCBP and men with partners of

childbearing potential must also use effective contraception during treatment; see Section 8.3 for details.
- Blood samples for hematology and chemistry will be obtained; urine samples will be obtained for urinalysis and drug testing.
- Allergic status will be documented by skin prick testing against common airborne allergens (e.g., cat, dust mite, grass, pollen).
- An S-STS will be conducted; subject score must be 0 to be eligible to enroll.

Visits 2, 3, and 4: ~Days -15, -14, -13

- Inclusion/exclusion will be assessed.
- AEs, concomitant medications, and ongoing medications will be recorded.
- Spirometry measurements will be taken.

3-Day Allergen Triad

Visit 2: Allergen skin titration (only if procedure was not previously performed at Visit 1), methacholine challenge, and sputum induction will be performed. At approximately 24 hours before the allergen challenge, subjects will be assessed for AHR by methacholine challenge (methacholine PC_{20} must be $\leq$ 16 mg/mL) and a sputum sample will be induced.

Visit 3: Allergen inhalation challenge and sputum induction will be performed. Subjects will be challenged with an allergen to which they tested positive on skin prick testing. Spirometry will be measured regularly until 7 hours post-allergen challenge and a sputum sample will be induced after the last spirometry measurement.

Visit 4: Methacholine challenge and sputum induction will be performed at approximately 24 hours post-allergen challenge.

Only subjects with a documented EAR and LAR to inhaled incremental allergen and methacholine challenges will be eligible for entry into Part 2 of the study.

Washout Period (2-4 weeks)

A rest/washout period will follow to confirm subject lung function and airway responsiveness (AHR) to methacholine has recovered (e.g., return of FEV_1 to within 90% of baseline and methacholine PC_{20} not more than 1 doubling dose lower than baseline). If more than 4 weeks is required, Sponsor Medical Monitor should be consulted.

10.2.2 Part 2 – Dosing/Treatment Period

Visit 5: Onsite Day 1 (predose)

- Review inclusion/exclusion criteria to verify eligibility to enter the dosing period.
  Note: If subject does not recover to an FEV_1 within 90% of baseline, additional washout time will be allowed, and the Visit 5 predose procedures may be repeated. If additional retest is required, the screening period may be extended beyond 4 weeks. If these criteria are met, sputum will be induced.
- Vital signs will be recorded.
- Spirometry measurements will be recorded.
- AEs, concomitant medications, and ongoing medications will be recorded.
- Blood samples for hematology and chemistry will be obtained.
- A urine sample for urinalysis will be obtained.
- WOCBP will have a urine pregnancy test performed; a negative result must be obtained before study drug treatment may be administered.
- A methacholine challenge will be performed; sputum will be induced.
- S-STS will be conducted.
- Dispensation of Meal and Daily Study Drug Dosing Diary.

Randomization and first dose: After predose assessments are conducted during Visit 5, subjects will be randomized (per IWRS) to receive zavegepant or placebo study treatment. Subjects will take their first prescribed dose onsite at the clinic and should continue to take their dose consistently at the same time of day, preferably once in the morning and once in the evening, through Visit 8. Each dose of study drug should be taken while fasting (e.g., at least 1 hour before breakfast/first meal of the day for the first dose, and at least 4 hours after the previous meal for the second dose). Subjects should not consume food other than water for 1 hour after dosing.

3-Day Allergen Triad

Visit 6: Onsite (pre-allergen challenge)

- Subjects will be asked to provide the time of their evening dose and meal on evening before this visit.
- After having fasted overnight; a blood sample for PK measurement will be collected for zavegepant concentration measurement (predose). Subjects will take the morning dose onsite at the clinic and should not consume food other than water for 1 hour after dose. Exact time of dosing and PK sample collection will be documented. Study procedures may begin immediately after dosing.
- Vital signs will be recorded.
- Spirometry measurements will be recorded.

- AEs, concomitant medications, and ongoing medications will be recorded.
- A methacholine challenge will be conducted; sputum will be induced postdose.
- Verification that subject is completing their Meal and Daily Study Drug Dosing Diary.

Visit 7: Onsite (allergen challenge)

- Subjects will be asked to provide the time of their evening dose and meal on evening before this visit.
- After having fasted overnight; a blood sample for PK measurement will be collected for zavegepant concentration measurement (predose).
- Subjects will take the morning dose onsite at the clinic and should not consume food other than water for 1 hour after dose. Study procedures may begin immediately after dosing.
- Allergen inhalation challenge will be conducted postdose in the morning; spirometry will be measured until 7 hours, and sputum will be induced 7 hours post-allergen challenge.
- Additional blood samples to measure zavegepant concentrations will be collected at approximately 1 (+ 0.5h) hour and 3 (+/- 0.5h) hours postdose. Exact times of dosing and PK sample collection will be documented.
- Vital signs and spirometry will be recorded.
- AEs, concomitant medications, and ongoing medications will be recorded.
- Verification that subject is completing their Meal and Daily Study Drug Dosing Diary.

Visit 8: Onsite (post-allergen)

- Subjects will be asked to provide the time of their evening dose and meal on evening before this visit.
- After having fasted overnight; a blood sample for PK measurement will be collected for zavegepant concentration measurement (predose). Subjects will take the morning dose onsite at the clinic and should not consume food other than water for 1 hour. Exact times of dosing and PK sample collection will be documented.
- Vital signs will be measured.
- Spirometry measurements will be performed.
- Pregnancy test conducted for WOCBP.
- Hematology, chemistry, and urine samples will be obtained.
- AEs, concomitant medications, and ongoing medications will be recorded.
- A methacholine challenge will be performed postdose in the morning (24 hours [± 3 hours] after the Visit 7 allergen challenge); sputum will be induced.
- Final S-STS will be conducted.
- Verification and collection of Meal and Daily Study Drug Dosing Diary.

10.2.3 Visit 9: Onsite (Follow-up)

- A physical examination will be performed, including BMI.
- A resting 12-lead ECG will be performed; subject should be in a resting, supine, or semi-recumbent position for at least 5 minutes.
- Clinical laboratory tests
- AEs, concomitant medications, and ongoing medications will be recorded.

10.2.4 Unscheduled Visit

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 8.6.

11 EFFICACY ASSESSMENTS

11.1 Efficacy, Clinical Performance, and Effectiveness

Spirometry and lung function will be assessed after each study dose treatment at Visit 5 through Visit 8 per Table 10-1. Methacholine PC_{20} and airway inflammation will be assessed before and after study dose treatment, and allergen-induced methacholine PC_{20}, allergen-induced bronchoconstriction, and allergen-induced airway inflammation will be assessed following allergen challenges.

11.1.1 Methacholine Inhalation Tests

Methacholine inhalation will be carried out using the method described by Cockcroft et al. and in accordance with AllerGen standard operating procedure (SOPs). A filter will be positioned on the exhalation-side of the 3-way valve to prevent methacholine from being nebulized/exhaled into the room. Briefly, methacholine is inhaled from a Hans Rudolf valve connected to a Wright nebulizer with an output of 0.13 mL/min. Subjects are instructed to wear nose clips and to breathe normally from the mouthpiece during the 2-minute inhalation period. Subjects inhale normal saline, then double concentrations of methacholine for 2 minutes. FEV_1 is measured at 30 and 90 seconds after each inhalation and, if necessary, at 180 and 300 seconds and beyond until the lowest response is captured. The test is terminated when a fall in FEV_1 of at least 20% (lowest post diluent FEV_1 versus lowest post methacholine concentration FEV_1) occurs, and the methacholine PC_{20} is calculated. The PC_{20} assessment will be performed at the start of each treatment period, then 24 hours before and 24 hours following allergen challenge as a measure of AHR.

11.1.2 Allergen Inhalation Challenge

Allergen inhalation challenge will be performed as described by O'Byrne (O'Byrne et al 1987), in accordance with AllerGen SOPs. The concentration of allergen extract for inhalation will be determined from a formula described by Cockcroft (Cockcroft et al 2005b). Doubling concentrations of allergen will be given until a 20% decline in FEV_1 is measured 10 minutes post-allergen inhalation versus baseline FEV_1. The FEV_1 will then be measured at regular intervals: 10, 20, 30, 45, 60, 90, 120 minutes, and 3, 4, 5, 6 and 7 hours after allergen inhalation to confirm both $\geq$ 20% fall in FEV_1 (EAR) and $\geq$ 15% fall in FEV_1 (LAR); the same final 3 doses of allergen administered during the screening period are administered during the dosing period challenge. The early bronchoconstrictor response (i.e., EAR) is taken to be the largest fall in FEV_1 within 2 hours after allergen inhalation, and the late response (i.e., LAR) is taken to be the largest fall in FEV_1 between 3 and 7 hours after allergen inhalation.

Allergen extracts manufactured following Good Manufacturing Practice (GMP) guidelines will be selected, prepared by study staff, and administered to the subjects by inhalation in accordance with procedures approved by Health Canada. Doubling concentrations of allergen will be

prepared by staff and administered to the subjects by the 2-minute tidal breathing inhalation method as described for methacholine and in accordance with procedures approved by Health Canada. A filter will be positioned on the exhalation-side of the 3-way valve to prevent allergens from being nebulized/exhaled into the room.

11.1.3 Sputum Induction

Sputum will be induced and processed using the method described by Pizzichini (Pizzichini et al 2002) and summarized. This procedure will be performed during the screening period at 24 hours before allergen challenges, and at 7 and 24 hours after allergen challenges, at the start of each treatment period, again at 24 hours before allergen challenges, and at 7 and 24 hours after allergen challenges. CCI [redacted] CCI [redacted]

11.1.4 Skin Testing

An allergy skin test, also called a skin prick test, will be used to determine the allergen that is given to each patient in the inhalation allergen challenge. It is performed by applying an extract of an allergen to the skin, scratching or pricking the skin to allow exposure, and then evaluating the local reaction in the skin. Standard allergen extracts for the following allergens will include, but are not limited to, ragweed, tree mix, grass mix, dog, cat, horse, feathers, dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*), Alternaria, and Aspergillus. A positive control (1 mg/mL histamine) and a negative control (diluent) are applied to the skin. If an allergen provokes an allergic reaction, a raised itchy bump (wheal) and redness (flare) develops. The size of the wheal (the raised area, not the redness) will be measured and recorded with a ruler in millimeters in the horizontal and vertical directions, perpendicular to each other after approximately 15 minutes. The size of the wheal for each antigen will be recorded on the Skin Test Form, along with any observed adverse reaction or event and any actions taken. A reaction greater than 2 × 2 mm will be regarded as positive, provided that the positive and negative controls are appropriately positive (histamine) and negative (diluent), respectively. The investigator will choose an allergen for inhalation on the basis of the largest skin response. This procedure will be completed in accordance with the CIC allergy skin testing by epicutaneous method (prick) SOP at McMaster University (Hamilton, Ontario, Canada).

11.1.5 Allergen Skin Titration

An allergy skin titration test is used to identify the lowest titration of allergen that causes a skin wheal at least 2 × 2 mm in size. It is performed by applying serial dilutions of a selected allergen extract to the skin, scratching or pricking the skin to allow exposure, and then measuring the skin's reaction with a ruler. The diameter of each wheal is measured in 2 perpendicular directions

after 10 minutes. The average wheal diameter for each dilution in the horizontal and vertical directions is recorded on the worksheet (i.e., 4 × 3 mm). The weakest dilution of allergen that produces an average wheal of at least 2 × 2 mm is the "skin test endpoint." This measurement is used to calculate the starting allergen dose for inhalation.

12 SAFETY ASSESSMENTS

12.1 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 IP, whether or not considered related to the IP.

AEs 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 abnormalities known to be associated with, and considered by the investigator to be a component of, the disease/syndrome.

The collection of non-serious AE information should begin from the time of informed consent through the follow-up period (7 to 10 days after last visit). Non-serious AE information should also be collected from the start of a placebo lead-in phase or other observation period intended to establish a baseline status for a subject.

Unchanged, chronic conditions, or those related to the underlying disease or medical conditions that are consistent with natural disease progression are not considered AEs and should not be recorded on AE pages of the eCRF unless there is an exacerbation of a chronic condition.

Definition of terms related to all Adverse Events (both 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.

Assessment for Determining Relationship of AE to Study Drug:

The relatedness of each AE to study drug must be classified based on medical judgment and according to the following categories:

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 2 types of AEs: SAEs and non-serious AEs.

12.2 Serious Adverse Events

SAEs will be collected from the time of informed consent and for the duration of the study. SAEs and AEs listed in the Sponsor's IB will be considered expected events. See the Sponsor IB for additional details of drug expected AEs.

12.2.1 Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria at any dose:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect.
- 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 12.2.5)
    - 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 feeling 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 12.2.4.

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.

12.2.2 Collection and Reporting of 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 at follow-up, up to 10 days after last dose treatment. The investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

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.

All SAEs, whether considered related or not related to study drug, overdose, potential drug induced liver injury (DILI), or pregnancy, 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/REB as per the reporting requirements. Additionally, the investigator, or designated staff, is responsible for entering the SAE information into the eCRF with event term, start/stop dates, causality, and severity.

For this study, SAEs will be captured through electronic data capture (EDC) and on the SAE report form. Any SAE must be reported immediately (or no later than 24 hours after awareness of the event) to Pharmaceutical Product Development (PPD) Pharmacovigilance (PVG) using the SAE report form and transmitted by facsimile (fax), which is the preferred method of submission:

- North America – 1-888-488-9697

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

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 (BHV-3500-204)
- SAE term (if an SAE is being reported)

12.2.3 Pregnancy

Following the baseline visit or at any time during the study it is discovered that a subject is pregnant or may have been pregnant at the time of the study drug exposure, including during at least 6 half-lives after study drug administration, the study drug 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 by the subject (i.e., follow-up procedures per Table 10-1).

12.2.3.1 Reporting of Pregnancy

Sites should instruct patients to contact the investigator if they become pregnant during the course of the study. The investigator must immediately notify the Biohaven Medical Monitor (or designee) of the event and complete the Pregnancy Report Form in accordance with SAE reporting procedures as described in Section 12.2.2. The pregnancy should be reported using paper forms, which should be faxed to PPD PVG, which is the preferred method of submission, within 24 hours after investigator/site awareness of the event:

North America – 1-888-488-9697

In the event the Pregnancy Report Form cannot be faxed or emailed, it must be reported via phone to the PPD Safety Hotline at:

North America – 1-800-201-8725

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 (or designee), and information on the pregnancy will be collected on the Pregnancy Report Form, as appropriate.

12.2.4 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 BHV-3500) 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 > 12 capsules instead of prescribed dose of 12 capsules in one calendar day) should be reported as a protocol deviation.

12.2.5 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrence of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 12.2.2.

Potential DILI is defined as:

1. ALT or AST elevation > 3 × the ULN

AND

2. Total bilirubin > 2 × the 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 decision of whether the subject must be discontinued from the trial and appropriate follow-up requirements.

12.3 Demographics and Medical History

Subject demographics will be recorded at screening and include date of birth (or age according to applicable regulations), sex, race, and ethnicity.

Medical history will also be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's pre-existing conditions, including all prior

significant illnesses, up to and including 5 years before screening. Additional pre-existing conditions present at the time when informed consent is given and up to the time of first dosing (Visit 5) are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

12.4 Vital Signs

Vital signs (body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 10-1). All vital signs will be measured after the subject has been resting in a sitting position for at least 10 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements determined by investigator judgment will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.5 Physical Examination

A complete physical examination (head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems) will be performed at the visits indicated in the Schedule of Assessments (Table 10-1).

Body weight (without shoes) will be recorded whenever physical examinations are recorded; height (without shoes) will be recorded and BMI will be calculated by the site at screening (Visit 1) only. All physical examinations will be performed by a physician.

Symptom-driven, limited physical examinations will be performed as clinically indicated at any study visit.

12.6 Electrocardiograms

A 12-lead, resting ECG will be measured in triplicate after the subject has rested in a supine or semi-recumbent position for 5 minutes or more at screening and at subsequent visits per Schedule of Assessments (Table 10-1). The ECG will be performed before spirometry.

At screening, the investigator will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented in the eCRF. Investigator

assessment of the abnormality will also be documented in the eCRF. Electrocardiograms will be repeated if clinically significant abnormalities are observed or artifacts are present.

12.7 Spirometry

Spirometry will be measured at time points in the Schedule of Assessments (Table 10-1), and after a physical examination and an ECG has been performed. Further, spirometry is used to monitor baseline lung function (safety and eligibility) and gauge level of bronchoconstriction during methacholine and allergen challenges.

12.8 Sheehan-Suicidality Tracking Scale

The S-STS is a prospective, clinician-administered rating questionnaire that tracks both treatment-emergent suicidal ideation and behaviors. The S-STS will be performed as outlined in Table 10-1.

This scale will be clinician-administered by a trained rater, completed onsite, and will be in paper format. The source document will be provided by the Sponsor. At the screening visit, the recall period for completing the S-STS will be the last 30 days prior; at all other visits, the recall period for completing the S-STS will be since the subject's last visit.

Subjects who have an S-STS score of > 0 should be evaluated by the investigator. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety must be made and mental health evaluation must be implemented. In such circumstances, the subject must immediately be discontinued from the study. The event should be recorded as determined by the investigator and reported within 24 hours to the Sponsor.

12.9 Clinical Laboratory Tests

Laboratory samples include, but are not limited to, assessments in Table 12-1, and are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 10-1).

Table 12-1. Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	albumin ALT ALP AST BUN or urea carbon dioxide creatinine eGFR creatine phosphokinase electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT glucose LDH total bilirubin direct and indirect bilirubin total cholesterol LDL HDL triglycerides	appearance pH protein glucose ketone bodies specific gravity urobilinogen bilirubin occult blood nitrates leukocytes
Pregnancy test: A human chorionic gonadotropin (hCG) blood test will be conducted on all WOCBP at screening; an hCG urine test will be conducted at all subsequent visits according to Table 10-1.		
Urine drug screen: Drugs of abuse include, but are not limited to, amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, and PCP (see Table 10-1). Retesting for positive results that are exclusionary is not allowed**.**		
Sputum test: Refer to Section 13.1 of protocol.		

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; GGT=gamma-glutamyl transpeptidase; Hb=hemoglobin; HBV=hepatitis B; Hct= hematocrit; HDL=high-density lipoproteins; LDH=lactate dehydrogenase; LDL=low-density lipoproteins; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PCP=phencyclidine; pH=potential hydrogen; RBC=red blood cell; WBC=white blood cell; WOCBP=women of childbearing potential.

Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. eGFR will be calculated using the estimated MDRD formula and reported by the central laboratory at each visit that chemistry tests are collected as outlined in Table 10-1.

Additional tests may be obtained to evaluate laboratory abnormalities and/or adverse events; please refer to the Laboratory Manual.

All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

13 OTHER ASSESSMENTS

[redacted]

[redacted]

14 PHARMACOKINETICS ANALYSIS

Blood samples for PK analysis of plasma zavegepant levels will be collected at the time points indicated in the Schedule of Assessments (Table 10-1). The actual date and time of each blood sample collection will be recorded.

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it if there are differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

15.1 Determination of Sample Size

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

Table 15-1 presents the 95% confidence intervals (CIs) for observed differences between treatment in maximum percentage decrease in LAR FEV_1.

Table 15-1. Confidence Intervals (95%) for Observed Differences Between Zavegepant and Placebo in Maximum Percentage Decrease in Late Asthmatic Response (LAR) Forced Expiratory Volume in 1 Second (FEV_1)

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

Abbreviations: CI=confidence interval; FEV_1= forced expiratory volume in 1 second; LAR=late asthmatic response.

15.2 Analysis Populations

Enrolled population: The enrolled population will include all subjects who sign the ICF and are assigned a subject identification number.

Randomized population: Enrolled subjects who receive a randomization treatment assignment from the IWRS.

Treated population: Randomized subjects who received at least 1 dose of study therapy.

Modified Intent-to-Treat (mITT) population: Randomized subjects that received at least 1 dose of study therapy and provided at least 1 non-missing post-baseline LAR assessment.

15.2.1 Analysis of Primary Efficacy Endpoints

The LAR, as assessed by maximum percentage decrease in FEV_1 between 3 and 7 hours post-allergen challenge, will be compared between zavegepant and placebo using analysis of covariance (ANCOVA), with treatment group as main variable and respective baseline LAR value as covariate. Point estimate, 95% CIs, and 2-sided p-value will be reported for the difference in LARs comparing zavegepant and placebo.

The LAR will also be assessed by AUC for the percent decrease in FEV_1 between 3 and 7 hours, using similar methods as above.

Additional supportive endpoints, including minimum absolute FEV_1 value in 3 to 7 hours and AUC of the absolute FEV_1 values in 3 to 7 hours, will also be similarly analyzed.

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

15.2.2 Analysis of Secondary Efficacy Endpoints

The EAR, as assessed by maximum percentage decrease in FEV_1 between 0 and 2 hours post-allergen challenge, (AUC for the percent decrease in FEV_1 between 0 and 2 hours, minimum absolute FEV_1 value in 0 to 2 hours, AUC of the absolute FEV_1 values in 0 to 2 hours) will be analyzed using the same methods as for primary endpoint.

The methacholine PC_{20} will be normalized by log transformation. Pre- and post-allergen challenge methacholine PC_{20} will be summarized with geometric mean and range. The pre- versus post-allergen shift in PC_{20} will be compared between zavegepant and placebo with baseline shift as covariate. The methacholine PC_{20} will be presented graphically.

CCI

[redacted]

15.3 Safety Analysis

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version available at start of the study. The incidence of treatment-emergent

AEs (TEAEs; events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. Treatment-related AEs, SAEs and AEs causing discontinuation will be tabulated. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

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

Clinical laboratory data and vital signs will be summarized using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated during the study period.

15.4 Interim Analysis

No interim analysis is planned for this study.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH), and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

16.1.2 Institutional Review Board/Research Ethics Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/REB/independent ethics committee (IEC). Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets, and other subject-facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the investigator or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The investigator will provide the Sponsor or its representative with a copy of the IRB-/REB-/IEC-approved ICF before the start of the study.

16.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such

that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based EDC system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IRBs/REBs/IECs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

16.4 Record Retention

Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the study drug in this trial has received its last approval for sale, or at least 2 years after the study drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the Sponsor's monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits, both onsite and remote (telephone call), will be outlined in the study monitoring plan. The investigator will assure he/she and adequate site personnel are available

throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/REB/IEC for information only. The Sponsor will ensure that acknowledgment is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/REBs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/REB/IEC and in accordance with applicable regulatory authority mandates is an investigator responsibility.

All protocol deviations will be identified, evaluated, and closed before the respective database lock (final analysis) and will be described in the clinical study report.

Protocol deviations incurred as a direct result of the COVID-19 pandemic should be specifically recorded as a "COVID-19" deviation so that they can be easily identified and incorporated into the clinical study report.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IECs/REBs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy and Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

17 REFERENCES

1. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. *J Headache Pain*. 2020;21(1):23. doi: 10.1186/s10194-020-1084-y
2. Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: comparison of two methods. *Chest*. 2005a;127(3):839-844. doi: 10.1378/chest.127.3.839
3. Cockcroft DW, Davis BE, Boulet L-P, et al. The links between allergen skin test sensitivity, airway responsiveness and airway response to allergen. *Allergy*. 2005b;60(1):56-59. doi: 10.1111/j.1398-9995.2004.00612.x
4. Ding W, Stohl LL, Xu L, et al. Calcitonin gene-related peptide-exposed endothelial cells bias antigen presentation to CD4+ T cells toward a Th17 response. *J Immunol* 2016;196(5):2181-2194. doi: 10.4049/jimmunol.1500303
5. Table of Substrates, Inhibitors and Inducers. US Food & Drug Administration website. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table%203-2. Table 3-2, Table 3-3, and Table 5-2. Accessed March 24, 2021.
6. Global Initiative for Asthma (GINA). Interim guidance about COVID-19 and asthma, updated 20 Dec 2020. https://ginasthma.org
7. Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010 Oct;5(1):61-72. doi: 10.1186/1479-7364-5-1-61. http://www.druginteractionsolutions.org
8. Kay AB, Ali FR, Heaney LG, et al. Airway expression of calcitonin gene-related peptide in T-cell peptide-induced late asthmatic reactions in atopics. *Allergy*. 2007;62(5):495-503. doi: 10.1111/j.1398-9995.2007.01342.x
9. Kim B-G, Park M-K, Lee P-H, et al. Effects of nanoparticles on neuroinflammation in a mouse model of asthma. *Respir Physiol Neurobiol*. 2020;271:103292. doi: 10.1016/j.resp.2019.103292
10. Mikami N, Watanabe K, Hashimoto N, et al. Calcitonin gene-related peptide enhances experimental autoimmune encephalomyelitis by promoting Th17-cell functions. *Int Immunol.* 2012;24(11):681-691. doi: 10.1093/intimm/dxs075
11. O'Byrne PM, Hargreave FE, Kirby JG. Airway inflammation and hyperresponsiveness. *Am Rev Respir Dis*. 1987;136(4 Pt 2):S35-S37. doi 10.1164/ajrccm/136.4_Pt_2.S35
12. Pizzichini E, Pizzichini MM, Leigh R, Djukanović R, Sterk PJ. Safety of sputum induction. *Eur Respir J Suppl*. 2002;37:9s-18s. doi:10.1183/09031936.02.00000902
13. Springer J, Amadesi S, Trevisani M, et al. Effects of alpha calcitonin gene-related peptide in human bronchial smooth muscle and pulmonary artery. *Regul Pept*. 2004;118(3):127-134. doi: 10.1016/j.regpep.2003.11.006

14. Sui P, Wiesner DL, Xu J, et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science*. 2018;360(6393):eaan8546. doi: 10.1126/science.aan8546
15. Tränkner D, Hahne N, Sugino K, Hoon MA, Zuker C. Population of sensory neurons essential for asthmatic hyperreactivity of inflamed airways. *Proc Natl Acad Sci U S A*. 2014;111(31):11515-11520. doi: 10.1073/pnas.1411032111
16. Vazegepant (BHV-3500) Investigator's Brochure. Version No. 4.0, dated 24 Nov 2020.