Official Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis - The ASPEN Study

NCT Number: NCT04594369

Document Date: Protocol Version 7: 14 Feb 2024

Signature Page for INS1007-301 Version 7.0 Global Protocol Amendment 4

Approve	[redacted] 14-Feb-2024 13:16:54 GMT+0000

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis – The ASPEN Study

Study Number INS1007-301

IND Number: 133790
EudraCT Number: 2020-003688-25
ClinicalTrials.gov Identifier: NCT04594369

Insmed Incorporated
700 US Highway 202/206
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	Version Number	Amendment	Date
Global Amendment 4	7.0	4	13 FEB 2024
Global Amendment 3	6.0	3	09 AUG 2022
Global Amendment 2	5.0	2	07 DEC 2021
Global Amendment 1	4.0	1	12 MAR 2021
Original Protocol	1.0		31 JUL 2020

INVESTIGATOR'S AGREEMENT

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis – The ASPEN Study

Investigator's Signature:

I have read and understood the current version of the protocol (as listed above).

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject to obtain consent.

I agree to conduct this study per this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, the International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6 [R2] GCP), and applicable local laws, regulations and guidelines.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records to verify the data that I have entered into the case report forms. I am aware of my responsibilities as an Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

IMPORTANT CONTACTS

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Version[a]**	**Date**
Global Amendment 4	7.0	13 FEB 2024
Global Amendment 3	6.0	09 AUG 2022
Global Amendment 2	5.0	07 DEC 2021
Global Amendment 1	4.0	12 MAR 2021
Original Protocol	1.0	31 JUL 2020

[a] Versions 2.0 and 3.0 are country-specific amendments.

Version 7.0, Global Amendment 4, (13 FEB 2024)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes in Global Amendment 4 is an update to the duration of the interval for defining a separate pulmonary exacerbation event. This change is the result of further evaluation based on Health Authority feedback and external development programs.

Grammatical and typographical errors as well as internal inconsistencies have been corrected throughout the document.

A summary of major changes in this amendment compared to Global Amendment 3 is presented in the table below.

Revision	Rationale	Location of Revision
Updated the duration of the interval for defining a separate pulmonary exacerbation event: At least 2 weeks (14 days) must occur between the end date of an earlier PE and the start date of the next PE for the PEs to be considered separate events.	To align with Health Authority feedback and evaluation of external development programs	• Section 7.1 • Section 10.4.6.1.1
Updated the multiplicity control procedure of truncated Hochberg procedure to the enhanced mixture-based gatekeeping procedure with the primary endpoint and all secondary endpoints tested at alpha of 0.05 with primary endpoint also being tested at alpha of 0.01.	To enhance the overall type I error rate control for the primary and secondary endpoints	• Synopsis • Section 10.4.6.1.2 • Section 10.4.6.2.1 • Section 10.4.6.4

Revision	Rationale	Location of Revision
Clarified analysis for adult-only subgroup	To align with Health Authority feedback	• Section 10.4.6.5
Added age group (adult, adolescent) as a potential covariate in the primary analysis model for the primary endpoint	To align with Health Authority feedback	• Synopsis • Section 10.4.6.1.2
Removed safety estimand	To remove unnecessary specification of safety estimand while the analyses remain unchanged as descriptive summary by each treatment group	• Synopsis • Section 2.2 • Section 10.4.7
Updated end of study reference to end of Week 52 treatment period	To fix typo and maintain consistency with statistical sections	• Synopsis • Section 7.1
Updated “Nonwhite” race to specific subcategories	To align with agency guidances	• Section 10.4.6.5
Corrected footnoting in Schedule of Assessments and Procedures Table	The footnoting associated with V11 and V12 has been corrected from “v” to “w”	• Table 5
Updated language for sample collection for biomarkers in sputum	Removed "for substudy subjects only" and "for all newly enrolled and substudy subjects only", as this text is not applicable in the bulleted list	• Section 8.4.1
Updated the percentages regarding subject enrollment	The enrollment target for North America, Western Europe, Asia Pacific and Latin America, and the enrollment cap for any single country (except the US) was increased to support implementation	• Synopsis • Section 1.5 • Section 3.1 • Section 5.2 • Section 10.1

PROTOCOL SYNOPSIS

IND Number: **EudraCT Number:**	**133790** **2020-003688-25**
Protocol Number:	INS1007-301
Amendment Number:	Version 6.0, Global Amendment 3
Investigational Product:	Brensocatib (INS1007) oral tablets
Active Ingredient(s)/INN:	Brensocatib
Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis – The ASPEN Study
Study Phase:	3
Indication Under Investigation:	Non-cystic fibrosis bronchiectasis

Objectives and Estimands:

Unless otherwise noted, for each of the estimands described below, the population comprises subjects with non-cystic fibrosis bronchiectasis (NCFBE). The treatment regimen is standard of care plus randomized investigational product (ie, study treatment; brensocatib 10 mg once daily [QD], brensocatib 25 mg QD, or placebo) and/or addition of chronic antibiotic (efficacy estimands).

The efficacy objectives will utilize a treatment policy strategy for handling of intercurrent events (ICEs) related to early discontinuation of randomized IP, early discontinuation from standard of care, and related to addition of chronic antibiotics (ICH E9(R1) Addendum).

Objective	Variable (or Endpoint)	Population Level Summary
Primary		
To evaluate the effect of brensocatib at 10 mg and 25 mg compared with placebo on the rate of pulmonary exacerbations (PEs)	Annualized rate of PEs	Rate ratio
Secondary		
To evaluate the effect of brensocatib compared with placebo on	Time to first PE	Hazard ratio
	Responder status for exacerbation free	Odds ratio
	Change in postbronchodilator forced expiratory volume in 1 second (FEV_1) at Week 52	Mean difference
	Annualized rate of severe PEs	Rate ratio
	Change in QOL-B Respiratory Symptoms Domain Score at Week 52 Population: adult subjects	Mean difference

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To evaluate the effect of brensocatib compared with placebo on	Adverse events	—
	Clinical laboratory parameters, vital signs, and ECG	—
To evaluate brensocatib exposure in adults and adolescents	Brensocatib plasma concentrations over time	—

See Section 2.3 for exploratory objectives and endpoints.

Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study to assess the efficacy, safety, and tolerability of 2 dosage strengths of brensocatib compared with placebo in subjects with non-cystic fibrosis bronchiectasis (NCFBE). Approximately 1620 adult subjects, defined as subjects ≥18 to ≤85 years of age, will be randomized in a 1:1:1 ratio to 3 treatment arms (540 subjects per arm) to receive brensocatib 10 mg once daily (QD), brensocatib 25 mg QD, or matching placebo QD for 52 weeks.

- Randomization will be stratified based on geographic region (North America, Europe, Japan, and the Rest of the World), sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, and the number of prior PEs (2, or ≥ 3) in the previous 12 months.
- Randomization will be enforced to have approximately 30% of adult subjects with 3 or more prior PEs, to have no more than 20% of subjects older than 75 years of age, to have approximately no more than 20% of subjects with eosinophil count in peripheral blood ≥300/mm^3 at Screening, and to have no more than 20% of subjects with COPD as comorbidity.
- Enrollment targets have been established for adult subjects with up to 13% of subjects from Eastern Europe and with North America, Western Europe, Asia Pacific, and Latin America contributing between 20% and 30% each. No single country (except the US) will contribute more than 15% of the overall randomized population.

For this study, the adolescent population is defined as subjects ≥12 to <18 years of age at Screening. Adolescent subjects are required to have at least 1 PE in the prior 12 months. Approximately 40 adolescent subjects will be randomized in a 2:2:1 ratio to 3 treatment arms (16:16:8 subjects per arm, respectively) to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or matching placebo QD for 52 weeks. Sputum sample will be classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit. Subjects in this age group who are not able to produce a sputum sample will be marked as negative. No stratification will be applied to this age group.

During the study, subjects will be assessed for PEs and will undergo clinical laboratory tests, PK and PD evaluations (adults only), vital sign measurements, patient-reported outcome measures, collection of the days of work and/or school missed due to PE, and collection of healthcare visit information.

This study will also include 2 substudies:

- Pharmacokinetic/pharmacodynamic (PK/PD) substudy - The substudy will include approximately 300 adult subjects who are not receiving cyclic antibiotics at Baseline and from whom additional blood PK and sputum PD samples will be collected, with blood PD samples collected from approximately 40 of these subjects. Blood PK and sputum PD samples will be collected from all adolescent subjects who are not receiving cyclic antibiotics at Baseline (blood PD samples will not be collected from adolescent subjects).
- Computed tomography (CT) scan substudy - The substudy will include approximately 225 adult subjects who will undergo high-resolution CT scanning at Screening and End of Treatment.

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Study Duration:

The maximum study duration is 62 weeks total for an individual participant, including a Screening Period of up to 6 weeks, a treatment period of 52 weeks, and an End of Study Visit 4 weeks following the end of treatment.

Study Sites and Locations:

The subjects in this study will be enrolled at over 400 study sites located in North America, Europe, Japan, and the Rest of the World.

The adolescent subjects will be enrolled in participating countries and sites where local regulations, countries, and/or institutional policies allow for patients <18 years of age to participate.

Subject Eligibility Criteria:

Key Inclusion Criteria:

- Adult subjects
  - Provided their signed informed consent
  - Male or female ≥18 years and ≤85 years of age
  - Body mass index ≥18.5 kg/m^2 at Screening (Visit 1)
  - Clinical history consistent with NCFBE confirmed by chest CT
  - At least 2 PEs in the past 12 months
- Adolescent subjects
  - Provided their signed assent (if required per local requirements) and parent or legal guardian provided their signed informed consent
  - Male or female ≥12 to <18 years of age at Screening in participating countries and sites where local regulations, countries, and/or institutional policies allow for patients <18 years of age to participate
  - Body weight ≥30 kilograms at Screening
  - Clinical history consistent with NCFBE confirmed by chest CT
  - At least 1 PE in the past 12 months
- For more comprehensive details of the inclusion criteria, refer to Section 4.1.1 of this protocol.

Key Exclusion Criteria:

- Subjects who have certain conditions or are receiving certain treatments that could adversely affect the subject's participation in the study, put the subject at unreasonable risk by participating in the study, or interfere with assessment of the effect of treatment will not be eligible for enrollment in the study.
- For more comprehensive details of the exclusion criteria refer to Section 4.1.2 of this protocol.

Study Treatment:

Study subjects will be assigned to 1 of 3 treatment arms. Based on treatment assignment, subjects will be supplied either brensocatib 10 mg oral tablets, brensocatib 25 mg oral tablets, or matching placebo oral tablets. Study treatment will be taken by subjects QD by mouth with water in the morning before breakfast.

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Sample Size Determination:

The study is designed to demonstrate superiority of brensocatib 10 mg and/or 25 mg over matching placebo as measured by the primary efficacy endpoint of the rate of PEs over the 52-week treatment period. Assuming the annualized PE rate in the placebo arm is 1.2 events with a negative binomial distribution with dispersion of 1, 1620 adult subjects will yield 90% power if the true exacerbation rate is 0.70 between any of the brensocatib treatment arms and placebo after 52 weeks of treatment. This estimate is based on study-wise two-sided Type I error of 0.01 or 0.005 for each primary comparison between brensocatib and placebo.

The adolescent sample size of approximately 40 subjects is based on the Sponsor's feasibility assessment as well as the prevalence of NCFBE in this age group. The sample size is expected to provide a description of the safety profile of brensocatib in this age group and offer the possibility to observe directional trends in efficacy.

Statistical Analyses:

The planned database lock is based on the time when the targeted 1620 adult subjects (originally planned sample size) complete the 52-week treatment period or discontinue from the study before Week 52. All adult and adolescent data collected up to this database lock will be included in the primary efficacy and safety analyses for the Clinical Study Report (CSR). Additional data collected between database lock and the last adolescent subject completing the last visit will be summarized in a CSR addendum. Additional analyses of efficacy and safety data will be detailed in the SAP.

Primary Endpoint

The primary efficacy endpoint is the annualized rate of PEs that have been confirmed through the event adjudication process.

The rate of PEs will be analyzed using the negative binomial model for the primary analysis when the last adult subject completes the 52-week treatment period. This analysis will be based on the Intent-to-Treat (ITT) Analysis Set. The model will include treatment group and randomization stratification factors (geographic region [North America, Europe, Japan, and the Rest of the World], sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, and the number of prior PEs in the previous 12 months), and age group (adult, adolescent) as fixed effects, and the time at risk (log scale) as an offset variable. The PE rate (PEs per subject per year) per treatment group, the ratios of PE rates between each brensocatib dose and placebo, and the associated 95% CIs will be estimated from the negative binomial model.

Secondary Endpoints

Secondary efficacy endpoints will be analyzed as follows:

- For time to first PE, the survival curves will be compared between the brensocatib dose and placebo using a Cox proportional hazards model based on the ITT Analysis Set. The covariate will include the stratification factors used for the randomization.
- For the proportion of subjects who are exacerbation free, the comparison between brensocatib and placebo will be analyzed using logistic regression with treatment group and randomization stratification factors as fixed effects.
- Absolute change from Baseline in postbronchodilator FEV_1 will be analyzed using a linear repeated measures model with fixed effects of treatment, stratification factors, visit, treatment-by-visit interaction, as well as the continuous, fixed covariate of Baseline value. An unstructured variance-covariance matrix will be fit.

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- The rate of severe PEs will be analyzed using the same method as the primary endpoint.
- The change from Baseline in QOL-B Respiratory Symptoms Domain Scores in the adult population will be analyzed using a linear repeated measures model with fixed effects of treatment, stratification factors, visit, treatment-by-visit interaction, as well as the continuous, fixed covariate of Baseline value. The variance-covariance structure will be compound symmetric with the robust sandwich variance estimator.

Safety endpoints including incidence and severity of treatment-emergent adverse events, clinical laboratory test results, vital signs, and electrocardiogram (ECG) will be descriptively summarized by treatment.

Brensocatib concentration data will be listed and summarized by dose level over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be listed. Individual and geometric mean plasma concentration-time data will be graphically displayed.

Adjustment of Multiplicity for Efficacy Analysis

In this study, the enhanced mixture-based gatekeeping procedure will be used as the multiplicity adjustment method to control the overall type I error rate at a full alpha ($\alpha = 0.05$) with a two-sided test for the multiple tests of the primary and secondary endpoints across the two brensocatib doses relative to placebo.

To demonstrate substantial evidence of effectiveness, the adjusted p-values for the comparisons of brensocatib 25 mg versus placebo and brensocatib 10 mg versus placebo for the primary endpoint, the annualized rate of PEs, will also be compared against the two-sided $\alpha = 0.01$.

Rejecting either or both null hypotheses and accepting the corresponding alternative hypotheses with lower rate of PEs in the brensocatib treatment arms, for the ITT Analysis Set, will be considered as a successful demonstration of efficacy.

Data Monitoring Committee and Other Committees:

An independent, external Data Monitoring Committee (DMC) will review all adverse events and serious adverse events to ensure the safety of subjects enrolled into this study. The DMC members will review the data in a semi-blinded or unblinded manner at predetermined intervals.

An independent adjudication committee composed of pulmonary physicians will adjudicate all reported PE events to determine if they fulfill the protocol definition.

An independent Steering Committee will be established to provide study oversight, including but not limited to the medical, scientific, operational, safety, and external communication of the study.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AA	Airway-Artery (method)
ABPA	allergic bronchopulmonary aspergillosis
AC	adjudication committee
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
ANC	absolute neutrophil count
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransaminase
ATS	American Thoracic Society
AUC	area under the concentration versus time curve
BCRP	breast cancer resistance protein
BE-CT	Bronchiectasis-Computed Tomography (score)
BEST	Bronchiectasis Exacerbation and Symptom Tool
BEST-CT	Bronchiectasis Scoring Technique for Computed Tomography
BMI	body mass index
BP	blood pressure
BSI	Bronchiectasis Severity Index
CatG	cathepsin G
CDC	Centers for Disease Control
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	maximum observed concentration
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
COVID-19	2019 corona virus disease
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
dECG	digital electrocardiogram
DICOM	Digital Imaging and Communications in Medicine

Abbreviation	Term
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPP1	dipeptidyl peptidase 1
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL-5 Dimension-5 Level Questionnaire
ER	emergency room
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
$FEF_{(25-75\%)}$	forced expiratory flow between 25% and 75% of forced vital capacity
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hy's Law
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IFN-γ	interferon gamma

Abbreviation	Term
IND	Investigational New Drug
INS1007	drug code for “brensocatib”
IRB	Institutional Review Board
IWRS	interactive web response system
LABA	long-acting beta agonist
LAM	lactational amenorrhea method
LAMA	long-acting muscarinic antagonist
LDH	lactic dehydrogenase
MAR	missing-at-random (assumption)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
MNAR	missing-not-at-random (assumption)
mPR3	membrane-bound proteinase-3
NCFBE	non-cystic fibrosis bronchiectasis
NE	neutrophil elastase
NOAEL	no-observed-adverse-effect level
NSP	neutrophil serine protease
NTM	nontuberculous mycobacteria
PCD	primary ciliary dyskinesia
PD	pharmacodynamic
PE	pulmonary exacerbation
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PGI-C	Patient Global Impression of Change scale
PGI-S	Patient Global Impression of Severity scale
P gp	P-glycoprotein
PHL	potential Hy’s Law
PLS	Papillon-Lefèvre syndrome
PK	pharmacokinetic
PMM	Pattern Mixture Model
$ppFEV_1$	percent predicted forced expiratory flow in 1 second

Abbreviation	Term
PR3	proteinase 3
PRO	patient-reported outcome
PT	Preferred Term
QD	once daily
QOL-B	Quality of Life Questionnaire - Bronchiectasis
QOL-PCD	Quality of Life instrument for Primary Ciliary Dyskinesia
QTcF	corrected QT interval by Fridericia's formula
RNA	ribonucleic acid
RR	respiratory rate
SABA	short-acting beta agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SAP	statistical analysis plan
SD	standard deviation
SFTP	Safe File Transfer Protocol
SOC	System Organ Class
SUSAR	suspected, unexpected serious adverse reaction
T	temperature
TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Non-Cystic Fibrosis Bronchiectasis

Non-cystic fibrosis bronchiectasis (hereafter referred to as NCFBE) is a chronic inflammatory disease defined by permanent dilatation of the bronchi (Barker, 2002). Subjects suffer from daily cough and sputum production and experience frequent exacerbations. The prevalence of NCFBE has steadily increased over the past 10 years in both the United States and Europe (Henkle et al., 2018; Quint et al., 2016). Despite an urgent need for treatment that can break the cycle of inflammation, infection, and irreversible progressive lung damage, there are no approved therapies specifically targeting this disease.

A European study (Lonni et al., 2015) included a total of 1,258 patients with NCFBE enrolled within the 7 centers (median age, 67 years; age range, 18–94 years; 40% males). Among the entire study population, the etiology of bronchiectasis was identified in 60% of patients (range among cohorts, 46%–82%). Excluding idiopathic bronchiectasis, the first 5 most commonly identified etiologies were post-infective (20%), COPD related (15%), connective tissue disease related (10%), immunodeficiency related (5.8%), and asthma related (3.3%). Of note, a significantly higher prevalence of COPD-related bronchiectasis was detected in patients with severe disease (22%) in comparison to those with mild disease (2.8%) and moderate disease (8.1%), according to BSI categories ($P<0.001$).

In a systematic review comprising 989 children with NCFBE from 12 studies, 63% of the subjects had an underlying disorder. Infectious diseases (17%), primary immunodeficiency (16%), aspiration (10%), ciliary dyskinesia (9%), congenital malformation (3%), and secondary immunodeficiency (3%) were the most common disease categories; 999 etiologies were identified. Severe pneumonia of bacterial or viral etiology and B cell defects were the most common disorders identified (Brower et al., 2014). In a recent study of 69 children with NCFBE at a center in the Netherlands, etiology was established in 91% of patients (n=63; median age 9 [3 to 18 years]). Post-infection (29%), and immunodeficiency (29%) were most common, followed by congenital anomalies (10%), aspiration (7%), asthma (6%), and PCD (1%) (Beckeringh et al., 2019).

1.2. Brensocatib

Brensocatib is being investigated in NCFBE for its potential role targeting neutrophil-mediated inflammation. Inflammation in bronchiectasis is dominated by neutrophils (Chalmers et al., 2017; Finch et al., 2019). Activation of neutrophils in the airway leads to release of NSPs, including NE, which is believed to be central to the pathophysiology of bronchiectasis (Chalmers and Chotirmall, 2018). Elevated NE, PR3, and CatG overwhelm natural inhibitors, such as alpha-1 antitrypsin and secretory leukoproteinase inhibitor (Dubois et al., 2012; Sibila et al., 2019), which leads to damaged airway walls (Chalmers and Chotirmall, 2018), mucus hypersecretion (Voynow et al., 1999), exacerbated inflammation (Finch et al., 2019), and disabled neutrophil and macrophage functions, increasing the risk of infection. NSPs are activated during neutrophil maturation in the bone marrow through the action of the enzyme DPP1, also known as cathepsin C. DPP1 removes the N-terminal dipeptide sequence of NSPs, allowing active enzymes to be packaged into granules prior to release into the circulation (Palmér et al., 2018).

Several factors may cause NCFBE, including severe respiratory infections (eg, bacterial pneumonia or tuberculosis), allergic bronchopulmonary aspergillosis, impairment of ciliary clearance (eg, primary ciliary dyskinesia), and primary or secondary immunodeficiency, and it may be associated with other diseases, such as COPD and severe asthma.

Subjects with NCFBE experience PEs with an average frequency ranging from 1.5 to 6 per year (Chalmers et al., 2014; Goeminne PC, 2014), and have poor quality of life. Frequent exacerbations of bronchiectasis are independently associated with worse quality of life, decreased lung function, and substantial morbidity and mortality (Barker, 2002; Chalmers et al., 2018; Quittner et al., 2015).

There is currently no therapy approved by regulatory authorities in the United States or Europe for the treatment of NCFBE. The primary goal of treatment is to treat the underlying cause, prevent disease progression, maintain or improve lung function, and improve the symptoms and quality of life.

Thus, the pediatric and adult populations differ significantly in the etiologies that cause the disease. Although infections are a common cause in both children and adults, pediatric age groups have a higher frequency of immune disorders compared to adults, in which the etiology of the disease is driven by other causes, including COPD and asthma. Despite these differences in etiology between adult and pediatric patients, the pathophysiology of NCFBE (once established in the airway) and the pharmacological rationale for brensocatib, are similar in adult and pediatric patients with NCFBE (Chalmers et al., 2017). Elevated levels of NE have been observed in children, which support extrapolation of efficacy and safety from adults with NCFBE to children with NCFBE.

Brensocatib ((2S)-N-{(1S)-1-cyano-2- [4-(3-methyl-2-oxo-2,3-dihydro- 1,3-benzoxazol-5-yl) phenyl] ethyl -1,4-oxazepane-2-carboxamide monohydrate) is a highly potent, selective, small molecule competitive and reversible inhibitor of DPP1 that is currently being developed for the treatment of NCFBE. Brensocatib (developed under the investigational product code INS1007) has been shown to inhibit NSP activity in blood in animal models and in healthy volunteers after 2 weeks to 1 month of dosing (Palmér et al., 2018). Treatment with brensocatib could therefore reduce neutrophilic inflammation in the systemic circulation and the lungs, leading to reduced risk of exacerbations in patients with NCFBE. Studies with naïve and lipopolysaccharide-induced pulmonary inflammation models in the rat showed that DPP1 inhibition with oral brensocatib translates well *in vivo*, as significant decreases in the activities of NSPs were observed.

1.2.1. Nonclinical Data

Human primary neutrophil studies showed that brensocatib significantly inhibits the activation of NSPs, resulting in decreased elastolytic ability of the cells *in vitro*. Furthermore, brensocatib produced concentration-dependent reduction in both the percentage of neutrophils with membrane-bound PR3 and the overall surface expression of PR3 in differentiating human neutrophils *in vitro*. Studies with naïve and lipopolysaccharide-induced pulmonary inflammation models in the rat showed that DPP1 inhibition with oral brensocatib translates well *in vivo*, as significant decreases in the activities of NSPs were observed.

Safety pharmacology studies of brensocatib showed no concerning cardiovascular, respiratory, or central nervous system effects at a notable safety margin to the systemic exposure in humans at a dose level of 40 mg.

The absorption, distribution, and metabolism of brensocatib have been studied *in vivo* in rat and dog and *in vitro* in mouse, rat, rabbit, dog, and human biomaterials. Brensocatib was highly bioavailable following oral administration in rats and dogs (75% and 92%, respectively). The fraction of unbound brensocatib in rat, dog, rabbit, mouse, and human plasma was 6.06%, 29.7%, 22.7%, 16.5%, and 12.8%, respectively. Quantitative whole-body autoradiography in the rat confirmed rapid absorption and widespread distribution of [^{14}C] brensocatib, with the highest concentrations associated with melanin-containing tissues. Pregnant rats showed evidence of fetal exposure. Slow metabolism of brensocatib were detected in rat, dog and human hepatocytes. A few minor metabolites detected (each less than 2% of total radioactivity) were mediated by CYP3A4/5 and no unique human metabolite was identified. *In vitro* evaluation at concentrations up to 30 μM showed that brensocatib did not inhibit CYP isozymes (IC_{50} >30 μM for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 and 3A4/5) nor induced CYP1A2, 2B6 and 3A4. Evaluation on transport inhibition showed that brensocatib did not inhibit solute carrier transporters, such as OATPs, OATs, and OCTs but had minor inhibitory effect on efflux transporters (IC_{50} > 11 μM), such as Pgp, BCRP, MATE1 and MATE2. Thus, at a clinically relevant concentration range, drug-drug interactions caused by brensocatib involving CYPs and transporters are unlikely.

The completed 6-month toxicology studies in rats and dogs are considered appropriate in support of including adolescent patients in the study, as the age of the animals at the start of the study was 6-7 weeks, and 5-6 months, respectively. This indicates that the animals at the start of the study entered puberty in both species (ICH S11). The completed 9-month dog study support clinical dosing beyond 6 months of duration.

1.2.2. Clinical Data

The clinical development program of brensocatib to date includes 2 completed Phase 1 studies conducted in healthy adult male volunteers (Study D6190C00001, Study D6190C00003), a completed Phase 1 study conducted in healthy male and female Japanese and Caucasian subjects (Study INS1007-101) and a completed Phase 2 study in subjects with NCFBE (Study INS1007-201).

1.2.2.1. Phase 1 Studies D6190C00001 (SAD/MAD Study) and D6190C00003 (Coadministered with CYP3A4 Inhibitors)

In Phase 1 Studies D6190C00001 and D6190C00003, brensocatib was well tolerated up to the highest dose levels assessed (single dose of 65 mg and multiple doses of 40 mg/day for 28 days). No trends were observed in clinical laboratory results, 12-lead ECGs, telemetry, physical examination, or spermatogram results. Abnormal findings observed in vital signs were not considered to be clinically significant. All TEAEs were mild or moderate, and the most common TEAE was headache (generally mild and considered related to the study treatment). There were no deaths or SAEs. Treatment discontinuation due to a TEAE was rare. Consistent with the protocol, 1 subject in Study D6190C00001 discontinued 25 mg/day brensocatib on Day 13 of a planned 28-day treatment period due to an AE of “drug eruption, lichen planus-like.” AEs of the

gingiva and skin of the palms and soles were of special interest with brensocatib because of their presence in Papillon-Lefèvre syndrome, a human genetic model of reduced DPP1 activity (Guarino et al., 2017; Pham et al., 2004; Sorensen et al., 2014). Mild skin and subcutaneous tissue disorders were observed in subjects receiving brensocatib.

In the presence of CYP3A4 inhibitors, the systemic exposure of brensocatib at 25 mg was not significantly affected. When coadministered with verapamil (240 mg), the C_{max} and AUC of brensocatib increased by 53% (592 vs 386 nmol/L) and 32% (8857 vs 6697 h*nmol/L), respectively. When coadministered with itraconazole (200 mg), brensocatib AUC increased by 14% (7615 vs 6697 h*nmol/L), while C_{max} decreased by 40% (234 vs 386 nmol/L). The elimination $t_{1/2}$ of brensocatib without or with coadministration of verapamil or itraconazole remained relatively unchanged (23.4, 20.4 and 27.9 hours, respectively).

1.2.2.2. Phase 1 Ethnic Pharmacokinetic Study INS1007-101

Study INS1007-101 was a two-part, randomized, double-blind, placebo-controlled Phase 1 study to evaluate the safety, tolerability, PK, and PD properties of single and multiple oral doses of INS1007, including ethnic PK assessment. Part A evaluated the safety, tolerability, PK, and PD of single and multiple oral doses of brensocatib in healthy adult Japanese and Caucasian subjects. Part B was an open-label, 2-period, and 2-sequence crossover food effect study.

Analysis of the effect of Japanese/Caucasian descent on brensocatib dose-normalized PK parameters showed that exposure was moderately greater for Caucasian subjects compared to Japanese subjects. On Day 1 (single dose), Japanese subjects had an approximately 12% (C_{max}) and 17% ($AUC_{0-\tau}$) lower geometric mean exposure. This pattern continued on Day 30 (multiple dose), as the Japanese subjects had an approximately 19% (C_{max}) to 26% ($AUC_{0-\tau}$) lower exposure.

For the Caucasian subjects, the AUC parameter increase with dose was more than dose-proportional on Day 1; by Day 30 the AUC increases were dose-proportional. C_{max} increased in a dose-proportional manner on both Day 1 and Day 30 for Caucasian subjects. For the Japanese subjects, the AUC and C_{max} parameters increased in a dose-proportional manner on Day 1 and Day 30.

A total of 65 TEAEs were reported in 37 of 82 subjects (45.0%), for Part A and Part B collectively, and of these, 27 TEAEs were reported in 19 of 40 Caucasian subjects (47.5%), and 38 TEAEs were reported in 18 of 42 Japanese subjects (42.9%). In Caucasian subjects, 25 TEAEs were reported in 17 of 40 subjects (42.5%) under fasted conditions, and 2 TEAEs were reported in 2 of 10 subjects (20.0%) under fed conditions. In Japanese subjects, 34 TEAEs were reported in 15 of 42 subjects (35.7%) under fasted conditions, and 4 TEAEs were reported in 3 of 9 subjects (33.3%) under fed conditions. The majority of TEAEs were of mild intensity; no severe TEAEs were reported. There were no deaths or other SAEs in this study.

The most frequently-occurring AESI overall was skin exfoliation (3 subjects [7.5%] in the pooled Caucasian group and 4 subjects [9.4%] in the pooled Japanese group). The next most frequently-occurring AESI was nasopharyngitis (2 subjects [5.0%] in the pooled Caucasian group, and 1 subject [2.4%] in the pooled Japanese group).

1.2.2.3. Phase 2 Clinical Study INS 1007-201

In a Phase 2, randomized, double-blind, parallel-group, placebo-controlled study, 256 subjects with a clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections) confirmed by chest CT were randomized (1:1:1) to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD for 24 weeks. Subjects were required to have ≥2 documented PEs in the past 12 months, a history of chronic sputum expectoration, sputum color at Screening rated as mucopurulent or purulent per validated color chart (Murray et al., 2009), and were able to provide a sputum sample during Screening.

Exacerbations during the study period were defined using a modified consensus definition (Hill et al., 2017). The primary endpoint was the time to first pulmonary exacerbation over the 24-week treatment period.

AESIs included periodontal disease and skin hyperkeratosis that were informed by the clinical presentation of PLS. All subjects, excluding those who were edentulous, underwent dental assessment at Baseline and at Weeks 8 and 24. Severe infections were also monitored as AESI.

Demographics and clinical characteristics at Baseline were similar across treatment groups; subjects were predominately Caucasian and female and over 60 years of age; 19% of subjects were >75 years at enrollment. Approximately 33% of subjects had 3 or more exacerbations in the previous 12 months.

The study achieved its primary endpoint of prolonging time to first pulmonary exacerbation for both brensocatib dosing strengths compared to placebo. Forty-two (42) subjects (48.3%) in the placebo group experienced an exacerbation compared to 26 subjects (31.7%) and 29 subjects (33.3%) in the 10 mg and 25 mg groups, respectively. The median time to first exacerbation in the placebo group was 189 days, while the median time to first exacerbation could not be estimated for either INS1007 group due to the low number of exacerbations in each group. The stratified log-rank test 1-sided *P* values for superiority for time to first exacerbation compared to placebo were *P*=0.014 and *P*=0.022 for the 10 mg and 25 mg groups, respectively. The unstratified log-rank test 1-sided *P* values were 0.010 and 0.028 for the 10 mg and 25 mg treatment groups respectively.

The proportion of subjects reporting any protocol-defined pulmonary exacerbation was significantly lower (Cochran-Mantel-Haenszel test) in the brensocatib 10 mg (26 subjects [31.7%]; *P*=0.017) and 25 mg (29 subjects [33.3%]; *P*=0.019) groups compared with placebo (42 subjects [48.3%]).

The annualized rates of PEs were significantly lower (negative binomial model) in the brensocatib 10 mg (0.80 [95% CI: 0.57, 1.12]) and 25 mg (0.96 [95% CI: 0.71, 1.30]) groups compared with placebo (1.25 [95% CI: 0.96, 1.63]).

The incidence of AEs and the number of subjects with a TEAE that led to study discontinuation were similar across treatment groups. Most TEAEs were mild to moderate. More subjects in the placebo group experienced a serious TEAE than in either INS1007 group. TEAEs leading to treatment and/or study discontinuation occurred once per Preferred Term with no obvious trends or relationship to treatment. Two subjects discontinued the study due to an AESI: placebo, n=1 (pneumonia); brensocatib 25 mg, n=1 (palmar erythema). One death (attributed to bronchiectasis

progression) occurred in a brensocatib 25 mg-treated [redacted]-year-old [redacted] with multiple comorbidities.

1.3. Study Rationale and Dose Justification

1.3.1. Study Rationale

Treatment with brensocatib is hypothesized to reduce levels of active NSPs in the sputum of patients with NCFBE, thus decreasing pulmonary inflammation and mucus hypersecretion, and consequently reducing the risk of PEs. The Phase 2 Study INS1007-201 investigated that hypothesis and demonstrated that brensocatib treatment reduced PEs and decreased inflammatory markers (eg, NE in sputum) in subjects with NCFBE over a treatment period of 24 weeks, as compared with placebo.

This study will investigate the efficacy, safety, and tolerability of brensocatib in the clinical management of subjects with NCFBE over 52 weeks. The goals are to confirm the findings from Study INS1007-201 and, if successful, to support marketing authorizations for brensocatib for the treatment of patients aged 12 years and older with NCFBE.

1.3.2. Dose Justification

Brensocatib has been studied using solution and tablet formulations in healthy volunteers, with dosing strengths ranging from 5 mg to 65 mg, and repeated administrations for 10 mg, 25 mg, and 40 mg across the formulations that support similar conclusions of dose proportionality. Phase 2 experience in subjects with NCFBE supports the efficacy of 6 months' exposure to 10 mg and 25 mg on reduction of PEs. Both doses demonstrated an acceptable safety profile as most TEAEs were mild to moderate in intensity across groups; those reported in ≥10% of brensocatib-treated subjects were cough, headache, increased sputum, and dyspnea, with some potential indication of dose dependency for events that may reflect DPP1 inhibition. Modeling and simulations using data from the Phase 2 study support that a reduction of sputum NE below quantification levels is associated with a reduction of exacerbations, and that such reduction is dose-dependent. The modeling and simulations did not support that lower doses were likely to yield equivalent efficacy to 10 mg nor that doses higher than 25 mg were likely to yield meaningful incremental efficacy. The current study therefore includes 10 mg and 25 mg as the two dosage strengths to be evaluated.

Using an adult population PK model, brensocatib exposure for adolescent patients at 10 and 25 mg was simulated based on the height and weight distributions for the age group reported by the Centers for Disease Control and Prevention (Kuczmarski et al., 2002). The simulated steady state AUC values were within the 95% CIs of those in adults with NCFBE for both dose levels (10 and 25 mg). This suggests that the adolescent subjects can receive the same dose levels of brensocatib as the adults and achieve a similar systemic exposure.

1.3.3. Study Population

The proposed study population will consist of adult male and female subjects diagnosed with NCFBE who are ≥18 years and ≤85 years of age and adolescent male and female subjects ≥12 to <18 years of age in participating countries and sites where local regulations, countries, and/or institutional policies allow for patients <18 years of age to participate. Subjects ≥18 years must

have a BMI ≥18.5 kg/m^2 at Screening. Adolescent subjects must have a body weight ≥30 kg at Screening. The goal is to randomize approximately 1620 adult subjects in a 1:1:1 ratio (540 subjects per treatment arm) and approximately 40 adolescent subjects in a 2:2:1 randomization scheme (16:16:8).

1.3.4. Treatment and Duration of Exposure

Approximately 1620 adult subjects and 40 adolescent subjects will be randomly assigned to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD for 52 weeks.

1.3.5. Efficacy Endpoints and Placebo Control

This study will assess the impact of brensocatib on the rate of PEs, lung function, and quality of life. Pulmonary exacerbations are key events in the natural history of patients with NCFBE and have the greatest impact on patient welfare, lung function, and healthcare utilization. Therefore, it is adequate to conduct the study in a double-blinded fashion, given that some of the endpoints incorporate patient symptomatology. This design will minimize biased responses based on knowledge of potentially receiving active agent(s) regardless of the study group to which a subject is randomized. A placebo comparator allows for the determination of the incremental benefit of brensocatib for this study population.

1.4. Benefits and Risks for Study Subjects

1.4.1. Potential Benefits

More detailed information about the known and expected benefits and risks and reasonably expected AEs of brensocatib is available in the Investigator's Brochure.

Brensocatib was previously investigated in a Phase 2 study in adult subjects with NCFBE (Study INS1007-201), during which subjects with NCFBE receiving brensocatib 10 mg or brensocatib 25 mg experienced statistically significant reductions in the occurrence of PEs on an annualized basis compared with subjects who received placebo (Section 1.2.2.3). Administration of brensocatib may result in beneficial effects for patients suffering from NCFBE via decreasing inflammation and mucus hypersecretion, leading to an improvement in respiratory symptoms (eg, cough and sputum production) and lung function (eg, FEV_1) and a decrease in exacerbation rate. Since brensocatib prevents maturation of NSPs, it may lead to a meaningful decrease of the inflammatory cascade.

1.4.2. Risks and Mitigation Strategies

Potential study subjects will be screened for study eligibility according to predetermined inclusion and exclusion criteria in order to ensure an appropriate benefit/risk balance for study participants and validity of efficacy and safety assessments. Procedures to ensure double-blinding of study drug and placebo will be in place. Measures to ensure validity of study efficacy results as well as subject safety will include specific guidance/prohibitions for use of concomitant medications and standardized safety reporting processes and procedures. A validated and well-defined primary efficacy endpoint has been established. Multiple safety assessments will be conducted; AESIs were predefined based on the mechanism of action for brensocatib (decreasing DPP1 activity) and safety findings from preclinical and clinical studies.

Procedures for detecting and reporting AESIs are specified in Section 9.10.3. Papillon-Lefèvre syndrome is a rare autosomal recessive disease characterized by mutations of the DPP1 gene and near complete loss of DPP1 function and NSP activity. Patients with PLS do not suffer from major infections; and their main symptoms include palmoplantar hyperkeratosis and severe periodontitis. Based on these known symptoms of PLS and brensocatib as a DPP1 inhibitor, the AESIs associated with exposure to brensocatib include hyperkeratosis (Section 9.10.3.1), periodontitis/gingivitis (Section 9.10.3.2), and infections (Section 9.10.3.3).

Overall, the aforementioned measures aim to provide an appropriate set of mitigation strategies to ensure the well-being of subjects enrolled in the trial.

1.5. Randomization and Blinding

In the adult population, upon meeting all inclusion criteria and none of the exclusion criteria, subjects will be randomized through IWRS (1:1:1) to brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD. The randomization will be stratified by: (a) region (North America, Europe, Japan, and Rest of World), (b) *Pseudomonas aeruginosa* culture status at Screening (positive or negative), (c) the number of PEs (2 or ≥3) in the prior 12 months. In addition, randomization will be enforced to have approximately 30% of adult subjects with 3 or more prior PEs, to have no more than 20% of subjects older than 75 years of age, to have approximately no more than 20% of subjects with eosinophil count in peripheral blood ≥300/mm^3 at Screening, and to have no more than 20% of subjects with COPD as comorbidity.

Enrollment targets have been established for adult subjects with up to 13% of subjects from Eastern Europe and with North America, Western Europe, Asia Pacific, and Latin America contributing between 20% and 30% each. No single country (except the US) will contribute more than 15% of the overall randomized population.

Adolescent subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized through IWRS (2:2:1) to brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo QD. There will be no stratification criteria applied to adolescent subjects.

Investigators and Sponsor will be blinded to treatment group assignments throughout the study. Unblinding is only to occur in the case of subject emergencies (Section 5.6) and at the conclusion of the study.

1.6. Treatment, Route, Dosage, Treatment Period

Eligible subjects with NCFBE who have signed the ICF (or assent form if required per local requirements) will receive treatment as follows:

- Brensocatib 10 mg QD, orally, before breakfast, for 52 weeks
- Brensocatib 25 mg QD, orally, before breakfast, for 52 weeks
- Matching placebo for brensocatib QD, orally, before breakfast, for 52 weeks

1.7. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki, the Council for International

Organizations of Medical Sciences, International Ethical Guidelines, ICH, GCP Guidelines, and applicable local regulatory requirement(s) and laws.

1.7.1. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Sponsor will observe the rules laid down in the European Data Protection Directive 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the eCRF or other documents submitted to Sponsor, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to Sponsor (eg, signed ICFs) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the EC or IRB direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

1.7.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 (R2) Guideline for GCP and any additional elements required by local regulations. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB/EC and by the health authority where applicable prior to being provided to potential subjects.

The subject's written informed consent (written or electronic) should be obtained prior to his/her participation in the study and should be documented in the subject's medical records, as required by applicable regulations. The ICF should be signed and personally dated by the subject or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject

or legal representative. The date that informed consent was given should be recorded in the eCRF.

Adolescent subjects must sign a study assent form (if required per local requirements) to participate in the study, and the subject's parent or legal guardian must sign and date a study-specific consent form. Adolescent subjects must be reconsented if they reach the age of majority during the study, in order to continue participating. The assent form (if required per local requirements) will comply with all applicable regulations governing the protection of human subjects. An assent form (if required per local requirements) must be approved by the IRB/EC and by the health authority, where applicable, prior to being provided to potential subjects.

1.7.3. Regulatory Compliance

The study protocol, subject information and consent form, adolescent assent form (if required per local requirements), the Investigator brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB/EC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

All protocol amendments and changes to the ICFs and assent form (if required per local requirements) or changes of the investigational site, facilities, or personnel (when applicable) must be submitted to the IRB/EC (and the health authority, if applicable), and where necessary, approval from the IRB/EC (and the health authority, if applicable) must be obtained. The Investigator should notify the IRB/EC of deviations from the protocol or SAEs occurring at the site and other AE reports received from the Sponsor, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND ESTIMANDS

The primary estimand for efficacy endpoints is the On-Study estimand. The treatment regimen in the On-Study estimand will be the randomized IP (ie, study treatment) plus standard of care taken up to 52 weeks irrespective of whether a new chronic antibiotic is added during the treatment period for prevention of future PE.

The supportive estimand for efficacy endpoints is the On-Treatment estimand as described in Section 10.4.6.1.4. The treatment regimen in the On-Treatment estimand for efficacy endpoints will include only the randomized study treatment plus standard of care taken up to 52 weeks without addition of new chronic antibiotics during the treatment period.

Additional details will be provided in the SAP.

2.1. Primary Objective and Estimand

The primary objective and estimand in subjects with NCFBE are presented in Table 1.

Table 1: Primary Objective and Estimand

Objective	Variable (or Endpoint)	Population Level Summary	Estimand Name	Treatment Regimen[a]	ICEs/Strategy
To evaluate the effect of brensocatib at 10 mg and 25 mg compared with placebo	Annualized rate of PEs	Rate ratio	Primary: On-Study	Standard of care + randomized IP and/or addition of a chronic antibiotic	Early discontinuation from randomized IP/ Treatment Policy Early discontinuation from standard of care/ Treatment Policy Addition of chronic antibiotics/ Treatment Policy

a Randomized IP (ie, study treatment) includes brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo in a 1:1:1 ratio for adult subjects and a 2:2:1 ratio for adolescent subjects.
PE = pulmonary exacerbation; ICE = intercurrent event; IP = investigational product

2.2. Secondary Objectives and Estimands

The secondary objectives and estimands in subjects with NCFBE are presented in Table 2.

Table 2: Secondary Objectives and Estimands

Objective	Variable (or Endpoint)	Population Level Summary	Estimand Name	Treatment Regimen[a]	ICEs/Strategy
Efficacy					
To evaluate the effect of brensocatib compared with placebo on	Time to first PE	Hazard ratio	Primary: On-Study	Standard of care + randomized IP and/or addition of a chronic antibiotic	Early discontinuation from randomized IP/ Treatment Policy Early discontinuation from standard of care/ Treatment Policy Addition of chronic antibiotics/ Treatment Policy

Objective	Variable (or Endpoint)	Population Level Summary	Estimand Name	Treatment Regimen[a]	ICEs/Strategy
	Responder status for exacerbation free	Odds ratio	Primary: On-Study	Standard of care + randomized IP and/or addition of a chronic antibiotic	Early discontinuation from randomized IP/ Treatment Policy Early discontinuation from standard of care/ Treatment Policy Addition of chronic antibiotics/ Treatment Policy
	Change in postbronchodilator FEV_1 at Week 52	Mean difference	Primary: On-Study	Standard of care + randomized IP and/or addition of a chronic antibiotic	Early discontinuation from randomized IP/ Treatment Policy Early discontinuation from standard of care/ Treatment Policy Addition of chronic antibiotics/ Treatment Policy
	Annualized rate of severe PEs	Rate ratio	Primary: On-Study	Standard of care + randomized IP and/or addition of a chronic antibiotic	Early discontinuation from randomized IP/ Treatment Policy Early discontinuation from standard of care/ Treatment Policy Addition of chronic antibiotics/ Treatment Policy
	Change in QOL-B Respiratory Symptoms Domain Score at Week 52[b]	Mean difference	Primary: On-Study	Standard of care + randomized IP and/or addition of a chronic antibiotic	Early discontinuation from randomized IP/ Treatment Policy Early discontinuation from standard of care/ Treatment Policy Addition of chronic antibiotics/ Treatment Policy
Safety					
To evaluate the effect of brensocatib compared with placebo on	Adverse events	—	—	—	—
	Clinical laboratory parameters, vital signs, and ECGs	—	—	—	—
Pharmacokinetic					
To evaluate brensocatib exposure in adults and adolescents	Brensocatib plasma concentrations over time	—	—	—	—

ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; ICE = intercurrent event; IP = investigational product; PE = pulmonary exacerbation; QoL-B = Quality of Life Questionnaire – Bronchiectasis.

a Randomized IP (ie, study treatment) includes brensocatib 10 mg QD, brensocatib 25 mg QD, or placebo in a 1:1:1 ratio for adult subjects and a 2:2:1 ratio for adolescent subjects.

b The population for change in QOL-B Respiratory Symptoms Domain Score at Week 52 will be adult subjects with NCFBE.

2.3. Exploratory Objectives and Endpoints

The exploratory objectives and endpoints are presented in Table 3.

Table 3: Exploratory Objectives and Endpoints

Objective	***Endpoint***
1. To evaluate the effect of brensocatib compared with placebo on daily symptoms, as assessed by the average daily BEST score over the 52-week treatment period	Average daily change from Baseline in BEST score over the 52-week treatment period
2. To evaluate the effect of brensocatib compared with placebo on the average duration of PEs over the 52-week treatment period	Duration of adjudicated PEs over the 52-week treatment period
3. To evaluate the effect of brensocatib compared with placebo on the number of days of hospitalization due to PEs over the 52-week treatment period	Days hospitalized due to adjudicated PEs per patient year over the 52-week treatment period
4. To evaluate the effect of brensocatib compared with placebo on the number of days of absence from work (or number of days of school absence in case the subject is of school age) due to PEs over the 52-week treatment period	Days of absence from work/school due to adjudicated PEs per patient year over the 52-week treatment period
5. To evaluate the effect of brensocatib compared with placebo on lung function, as measured by change in pulmonary function parameters including prebronchodilator and postbronchodilator FEV_1, FVC, PEFR, $ppFEV_1$, and $FEF_{(25-75\%)}$ over the 52-week treatment period	Change from Baseline in prebronchodilator and postbronchodilator FEV_1, FVC, PEFR, $ppFEV_1$, and $FEF_{(25-75\%)}$ at Weeks 16, 28, 40, 52, and over 52 weeks
6. To evaluate the effect of brensocatib compared with placebo on health care resource utilization (outpatient visits, ER visits, hospitalization for any reason) over the 52-week treatment period	Outpatient visits, ER visits, and hospitalizations for any reason
7. To evaluate the effect of brensocatib compared with placebo on quality of life, as assessed by the age-appropriate QOL-PCD domain scores over the 52-week treatment period in adolescent subjects (≥12 to <18 years of age) with PCD	Change in QOL-PCD domain scores from Baseline to Weeks 16, 28, 40, 52, and Over 52 Weeks in adolescent subjects (≥12 to <18 years of age) with PCD
8. To evaluate the effect of brensocatib compared with placebo on quality of life, as	Change from Baseline in EQ-5D-5L score from Baseline to Week 52

Objective	***Endpoint***
assessed by the EuroQoL-5D-5L over the 52-week treatment period	
9. To evaluate the effect of brensocatib compared with placebo on QOL, as assessed by the QOL-B domains over the 52-week treatment period in adult subjects	Change from Baseline in QOL-B domain scores to Weeks 16, 28, 40, and 52 in adult subjects
10. To evaluate the effect of brensocatib compared with placebo on PGI-S and PGI-C scales over the 52-week treatment period in adult subjects	Change in PGI-S and PGI-C from Baseline to Weeks 16, 28, 40, and 52 in adult subjects
11. To evaluate the effect of brensocatib compared with placebo on the rate of decline in prebronchodilator and postbronchodilator FEV_1 over the 52-week treatment period	Rate of change in prebronchodilator and postbronchodilator FEV_1 over the 52-week treatment period
12. To evaluate the effect of brensocatib compared with placebo on the progression of lung damage as evaluated by CT scan over the 52-week treatment period	Change from Baseline in BEST-CT and Airway-Artery scores at Week 52
13. To evaluate the effect of brensocatib compared with placebo on the concentration of biomarkers (NE, CatG, PR3) in sputum over the 52-week treatment period	Change in concentration of sputum NE, CatG, and PR3 from Baseline to Week 52
14. To evaluate the effect of brensocatib compared with placebo on the concentration of biomarkers (NE, CatG, PR3) and neutrophil functions in blood over the 52-week treatment period	Change in concentration of blood NE, CatG, PR3, and neutrophil functions from Baseline to Week 52
15. Population PK analysis	Estimated PK parameters (eg, C_{max}, AUC, $t_{½}$) using population PK analysis approach. Specified in a separate SAP
16. Population PK/PD relationship evaluation	Relationships between brensocatib exposure and response (safety, efficacy, and biomarker measurements) over the 52-week treatment period. Specified in a separate SAP

AUC = area under the concentration versus time curve; BEST = Bronchiectasis Exacerbation and Symptom Tool; BEST-CT = Bronchiectasis Scoring Technique for Computed Tomography; CatG = cathepsin G; C_{max} = maximum observed concentration; CT = computed tomography; ER = emergency room; EuroQoL-5D-5L and EQ-5D-5L = EuroQoL-5 Dimension-5 Level Questionnaire; $FEF_{(25\ 75\%)}$ = forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NE = neutrophil elastase; PD = pharmacodynamic; PE = pulmonary exacerbation; PEFR = peak expiratory flow rate; PGI-C = Patient Global Impression of Change scale; PGI-S = Patient Global Impression of Severity scale; PK = pharmacokinetic; $ppFEV_1$ = percent predicted forced expiratory flow in 1 second; PR3 = proteinase 3; QOL-B = Quality of Life Questionnaire - Bronchiectasis; QOL-PCD = Quality of Life instrument for Primary Ciliary Dyskinesia; SAP = statistical analysis plan; $t_{½}$ = half-life.

3. STUDY DESIGN

3.1. Overall Plan

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study to assess the efficacy, safety, and tolerability of 2 doses of brensocatib compared with placebo in subjects with NCFBE.

Approximately 1620 adult subjects will be randomized in a 1:1:1 ratio to 3 treatment arms (540 subjects per treatment arm) to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or matching placebo QD for 52 weeks. Randomization will be stratified based on the geographic region (North America, Europe, Japan, and the Rest of the World), sputum sample testing positive or negative for *Pseudomonas aeruginosa* at Screening Visit, and the number of prior PEs (2, or ≥3) in the previous 12 months. In addition, randomization will be enforced to have approximately 30% of adult subjects with 3 or more prior PEs, to have no more than 20% of subjects older than 75 years of age, to have approximately no more than 20% of subjects with eosinophil count in peripheral blood ≥300/mm^3 at Screening, and to have no more than 20% of subjects with COPD as a comorbidity. Enrollment targets have been established for adult subjects with up to 13% of subjects from Eastern Europe and with North America, Western Europe, Asia Pacific, and Latin America contributing between 20% and 30% each. No single country (except the US) will contribute more than 15% of the overall randomized population.

For this study, the adolescent population is defined as subjects ≥12 to <18 years of age at Screening. Approximately 40 adolescent subjects will be randomly assigned in a 2:2:1 ratio to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or matching placebo QD for 52 weeks. No stratification criteria will be applied to randomization of adolescent subjects.

All adult subjects will produce a sputum sample at the Screening Visit to evaluate the presence/absence of *Pseudomonas aeruginosa* as per the stratification criteria. Adolescent subjects will not be required to produce a sputum sample at the Screening Visit if they are unable to do so. Spontaneous or induced sputum is a reliable and accessible source of specimens for microbiological analysis in adults; however, collecting sputum from young children is problematic as they find it difficult to expectorate (Pizzutto et al., 2017). Adolescent subjects who are unable to produce a sputum sample will have their *P. aeruginosa* test result recorded as negative.

Subjects will receive instruction for entering data into electronic devices. After Baseline, subjects will return to the study site for in-clinic visits at Weeks 4, 16, 28, 40, 52 (EOT), and 56 (EOS), during which they will be assessed for PEs, and undergo clinical laboratory tests, PK and PD evaluations (adults only), vital sign measurements, and patient-reported outcome measures (Section 7.5). In addition, collection of the days of work and/or school missed due to PE will occur along with collection of healthcare visit information (eg, type of visit [hospitalization, doctor, or E R]), reason for visit, visit date). Telephone visits will occur at Weeks 10, 22, 34, 46, during which collection of AEs, concomitant medications, smoking status, periodontal complaints, patient-reported outcome measures (as mentioned above), urine pregnancy test results from WOCBP, and assessment for occurrence of PEs will occur. At Visit 11 (Week 52/EOT) subjects will discontinue all study treatment and will be followed for a 1-month follow-up period, during which initiation of any new medical or non-medical therapy for NCFBE

should be avoided. At Visit 12 (Week 56/EOS), subjects will complete all protocol-specified assessments and EOS procedures. The Schedule of Assessments is provided in Table 5.

PK/PD Substudy

The study will include a PK/PD substudy at select sites with proper laboratory capabilities. The substudy will include approximately 300 adult subjects who are not receiving cyclic antibiotics at Baseline and from whom additional blood PK and sputum PD samples will be collected, with blood PD samples collected from approximately 40 of these subjects. In addition, blood PK and sputum PD samples will be collected from all adolescent subjects who are not receiving cyclic antibiotics at Baseline (blood PD samples will not be collected from adolescents). Adult subjects must provide informed consent to participate in the PK/PD substudy and the blood PD aspect of the PK/PD substudy; the parent or legal guardian must provide informed consent for adolescent subjects.

Sample collections for each aspect of the PK/PD substudy are listed below:

- Blood PK component of the substudy: Blood samples for concentration of study drug will be collected as indicated in Appendix 5.
- Sputum PD component of the substudy: A sputum sample (approximately 3 mL) for NE, CatG, and PR3 concentrations will be collected as indicated in Appendix 6. Sputum induction is allowed for PD sputum sample collection except at Screening (Appendix 1). Adolescent subjects will not be required to produce a sputum sample if they are unable to do so.
- Blood PD component of the substudy (adult subjects in the US only): Blood samples for evaluation of NE, CatG, PR3 and other neutrophil functions will be collected as indicated in Appendix 6.

The PK/PD substudy is described in detail in Section 8.

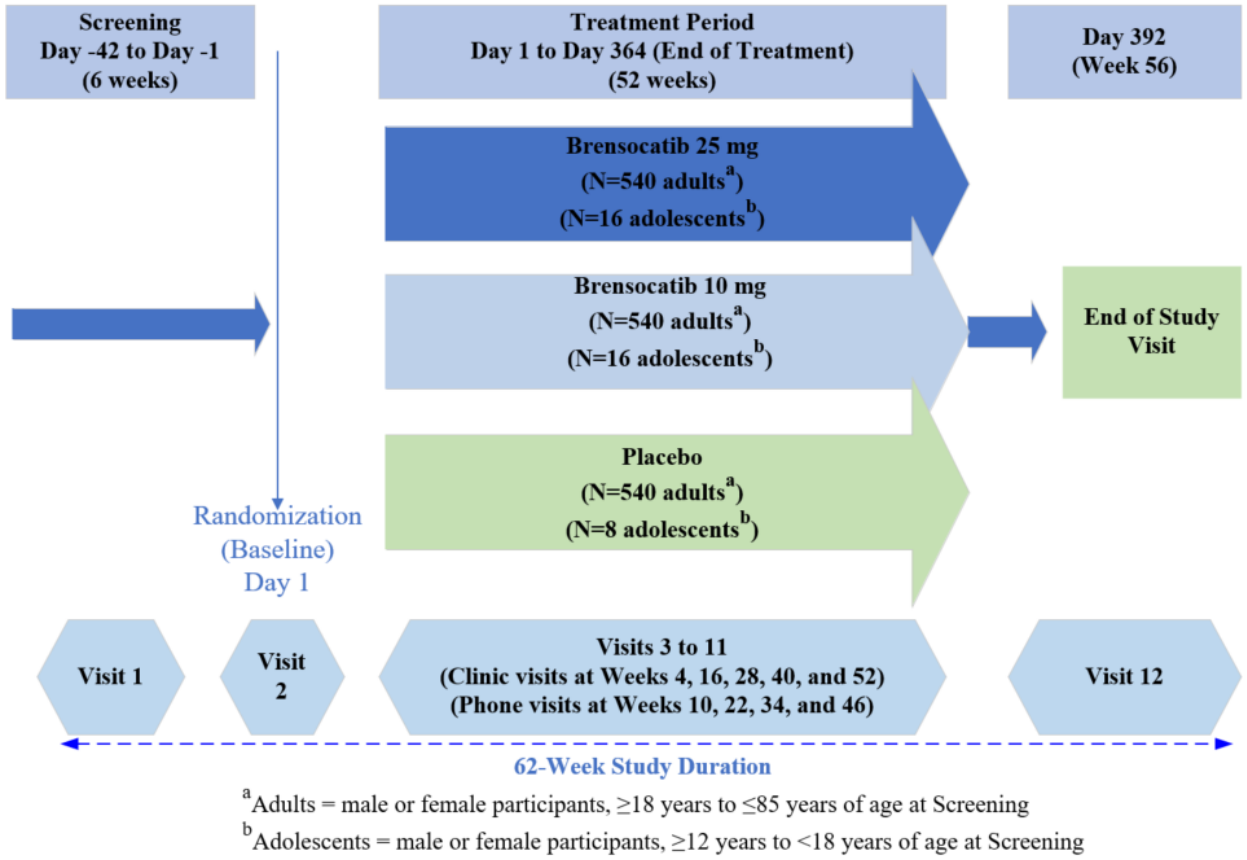
CT Scan Substudy

The study will also include a CT scan substudy with approximately 225 adult subjects. This substudy will include 2 study-specific high-resolution CT scans to be conducted at the Screening Visit and the Week 52 Visit as described in Section 7.6. Subjects must provide informed consent to participate in the CT scan substudy.

Please note: Participation in both the PK/PD and CT scan substudies is permitted; ie, participation in one of the substudies does not preclude participation in the other.

A study schematic is provided in Figure 1. The procedures and assessments conducted at each study visit in the study are provided in Table 5.

Figure 1: Schematic for Study INS1007-301



[a]Adults = male or female participants, ≥18 years to ≤85 years of age at Screening
[b]Adolescents = male or female participants, ≥12 years to <18 years of age at Screening

3.2. Data Monitoring Committee and Steering Committee

An independent, external DMC will be set up to review all AEs and SAEs to ensure the safety of subjects enrolled into this study. The DMC members will review the data in a semi-blinded or unblinded manner at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review those data. Further details of the DMC will be provided separately in the DMC Charter.

The primary endpoint parameter of this study is PE. An independent adjudication committee (AC) composed of pulmonary physicians will adjudicate all reported PE events to determine if they fulfill the protocol definition. Adjudication outcomes will be used in creation of analysis datasets. Details of the AC will be provided separately in the AC charter.

In addition, an independent Steering Committee will be established to provide study oversight including but not limited to the medical, scientific, operational, safety, and external communication of the study. Details of the Steering Committee will be provided separately in the Steering Committee Charter.

3.3. Duration of Subject Participation

The maximum study duration will be up to 62 weeks for an individual participant, including a Screening Period of up to 6 weeks, a treatment period of 52 weeks, and an EOS Visit 4 weeks following the end of treatment.

3.4. End of Study

The EOS visit date for analysis of subjects is defined as the date of the last visit for the last subject in the study.

A subject will be considered to have completed the study if he/she has completed all study visits, including the Week 52 Visit.

4. STUDY POPULATION

4.1. Enrollment

The subjects in this study will be enrolled at over 400 study sites located in North America, Europe, Japan, and the Rest of the World. The adolescent subjects will be enrolled in participating countries and sites where local regulations, countries, and/or institutional policies allow for patients <18 years of age to participate.

To be eligible for enrollment, subjects must meet all of the following inclusion criteria and none of the following exclusion criteria.

4.1.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Provide their signed study informed consent to participate.
    a. Adolescent subjects must have signed study assent form (if required per local requirements) to participate, and the adolescent's parent or legal guardian must have provided signed informed consent for the adolescent to participate
2. Male or female ≥18 years and ≤85 years of age at Screening.
    a. Adolescent subjects – male or female ≥12 to <18 years of age at Screening in participating countries and sites where local regulations, countries, and/or institutional policies allow for subjects <18 years of age to participate
3. Adult subjects must have a BMI ≥18.5 kg/m^2 at Screening.
    a. Adolescent subjects must have a weight of ≥30 kg at Screening
4. Clinical history consistent with NCFBE (cough, chronic sputum production and/or recurrent respiratory infections) that is confirmed by chest CT demonstrating bronchiectasis affecting one or more lobes (confirmation may be based on prior chest CT).
    a. For each subject, the most recent chest CT scan (but not older than 5 years before the Screening date) will be selected for transfer to the central reading facility for confirmation of the diagnosis of NCFBE.
    b. If the CT scan cannot be read by the reviewers due to quality issues, a new high-resolution CT scan will be performed.
    c. In case a chest CT scan in the last 5 years is not available, a new high-resolution chest CT scan must be obtained for confirmation of the diagnosis of NCFBE by the central reading facility.
5. Postbronchodilator FEV_1 at the Screening Visit ≥30% of predicted normal value, calculated using National Health and Nutrition Examination Survey reference equations and must have an absolute value ≥750 mL.
6. Adult subjects: Current sputum producer with a history of chronic expectoration of at least 3 months in the past 12 months, and able to provide sputum sample during Screening (Visit 1). If a subject is unable to produce sputum spontaneously during

Screening, the subject will be considered a screen failure. The subject should not undergo a sputum induction procedure during Screening to meet inclusion criterion.

a. Adolescent subjects are exempt from the requirement to provide a sputum sample if they are unable to do so and should not undergo a sputum induction procedure during Screening.

7. Mucopurulent or purulent sputum color assessed at the Screening Visit by color chart developed by MP Murray (Murray et al., 2009). Adolescent subjects who are unable to provide a sputum sample at Screening are exempt from this requirement.
8. At least 2 PEs defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before the Screening Visit.

   a. Adolescent subjects are required to have at least 1 pulmonary exacerbation in the prior 12 months

9. Women must be postmenopausal (defined as no menses for 12 months without an alternative medical cause), surgically sterile, or using highly effective contraception (ie, methods that can achieve a failure rate <1% per year when used consistently and correctly) from Day 1 to at least 90 days after the last dose. Such methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner. The Investigator or designee should explain the acceptable methods of birth control to the subject and instruct the subject to follow the direction. For WOCBP ≤45 years of age, testing of FSH level should be performed; a threshold of >40 mIU/mL should be met to be considered infertile.

   Note: Abstinence is only considered to be a highly effective method of contraception when this is the preferred and usual lifestyle of a subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

10. Male subjects with female partners of childbearing potential must be using effective contraception from Day 1 to at least 90 days after the last dose. Acceptable methods include true abstinence (refraining from intercourse during the study), combined (estrogen and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine devices, intrauterine hormone-releasing systems.
11. Male subjects with pregnant or non-pregnant WOCBP partners must use condoms to avoid potential exposure to the embryo/fetus.

4.1.2. Exclusion Criteria

Subjects are not eligible to participate in the study if they meet any of the following criteria:

1. A primary diagnosis of COPD or asthma as judged by the Investigator. Patients with comorbid COPD and/or asthma can be enrolled if bronchiectasis is their primary diagnosis.
2. Subjects receiving supplemental oxygen >12 hours per day.
3. Bronchiectasis due to cystic fibrosis.
4. Current smokers as defined per CDC: an adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.
5. No evidence of bronchiectasis according to the BE-CT scoring system.
6. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (eg, TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the Investigator.
7. Known history of HIV infection.
8. Established diagnosis of hepatitis B viral infection at the time of Screening, or positive for HBsAg at the time of Screening.

   Subjects who have gained immunity for hepatitis B virus infection after vaccination (subjects who are HBsAg-negative, HBsAb-positive, and HBcAb-negative are eligible for the study).

   Subjects with positive HBcAb are eligible for the study only if hepatitis B virus DNA level is undetectable.
9. Established diagnosis of HCV infection at the time of Screening. Subjects positive for hepatitis C antibody are eligible for the study only if HCV RNA is negative.
10. Currently being treated for NTM lung infection, allergic bronchopulmonary aspergillosis, or TB.
11. Active and current symptomatic infection by COVID-19.
12. Unable to perform technically acceptable spirometry that meet the ATS/ERS acceptability criteria with at least 3 acceptable flow-volume curves, at least 2 of which meet the ATS/ERS repeatability criteria for FEV_1 during Screening.
13. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).
14. Receiving medications or therapy that are prohibited as concomitant medications (see Section 5.11.1 for prohibited concomitant medications).
15. Started oral or inhaled antibiotics as chronic treatment for NCFBE <3 months prior to the Screening Visit.

a. Subjects on antibiotics as chronic treatment should be on such treatment for at least 3 months prior to Screening while meeting all other inclusion criteria and none of the exclusion criteria.

16. Chronic treatment with oral steroids (irrespective of the indication) is prohibited
17. Subjects who have adjustments to their baseline medications within 1 month before Screening; they can be rescreened a month after the new treatment has been initiated.
18. Abnormal renal function test result (eGFR <30 mL/min by Chronic Kidney Disease - Epidemiology Collaboration equation formula) at Screening.
19. Active liver disease or hepatic dysfunction manifested as follows:
    a. ALT or AST >3 × ULN.
    b. Total bilirubin >2 × ULN (isolated bilirubin >2 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    c. Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones.
    d. Child-Pugh class C.
20. History of malignancy in the past 5 years, except completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.
21. Previously participated in a clinical trial for brensocatib.
22. An absolute neutrophil count <1,000/mm^3 at the Screening Visit.
23. Received any live attenuated vaccine within 4 weeks prior to Screening. If a live vaccine has been administered the subject should wait 4 weeks prior to Screening. During the study, subjects may not receive any live attenuated vaccine.
24. Significant hemoptysis (≥300 mL or requiring blood transfusion) within 6 weeks prior to the Screening Visit or during the Screening Period.
25. Have diagnosed periodontal disease and are either:
    a. Currently treated by a dentist for this condition or
    b. Expected to have periodontal disease-related procedures within the study period.
26. Suffering an exacerbation 4 weeks before Screening or during the Screening Period. In this case, subjects will be considered a screen failure. Subjects are eligible for rescreen only after recovery and 4 weeks after last dose of antibiotic treatment (see Section 4.2.4, Subject Rescreening Procedures).
27. Adult subjects only: Have compliance issues with completion of electronic diary entries during the Screening Period and in the opinion of the Investigator, compliance is unlikely to improve during the study.
28. Participated in any other interventional clinical studies within 3 months before Screening Visit.
29. Clinical diagnosis of Papillon-Lefèvre Syndrome.

30. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the subject's participation in the study. Examples include but are not limited to short life expectancy, uncontrolled diabetes, cardiovascular conditions (eg, NYHA Class III or IV cardiac failure), severe renal conditions (eg, severe nephrotic syndrome), hepatobiliary conditions, neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinologic, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for subjects excluded under this criterion will be noted in study documents (chart notes, eCRF, etc.).
31. Any clinically significant abnormal laboratory values at Screening or diseases or disorders (eg, survivors of severe COVID-19 disease including ARDS, cardiovascular, pulmonary, gastrointestinal, liver, kidney, neurological, musculoskeletal, endocrine, metabolic, psychiatric, physical impairment, or a lung transplantation) that, in the opinion of the Investigator, may put the subject at risk by participating in the study, or interfere with the subject's treatment, assessment, or influence the results of the study, or have compliance issues with the study or have a planned or anticipated major surgical procedure during the study.
32. History of alcohol or drug abuse within 6 months prior to the Screening Visit.
33. Any other medical or psychological condition including relevant laboratory abnormalities at Screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study subject as a result of his/her participation in this clinical trial, may make subject’s participation unreliable, or may interfere with study assessments. The specific justification for subjects excluded under this criterion will be noted in study documents.
34. Is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
35. Known history of hypersensitivity to brensocatib or any of its excipients.

4.2. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

4.2.1. Discontinuation of Study Treatment

All subjects are encouraged to stay in the study regardless of study treatment discontinuation. Any subject who discontinues from the study treatment will have the reason for discontinuing treatment recorded and will be encouraged to continue to attend the remaining scheduled study visits and to complete patient-reported outcome measures assessed between study visits (Table 5, Section 7.5).

4.2.2. Participant Discontinuation/Withdrawal from the Study

A subject may decide to withdraw from the study at any time, for any reason. The Investigator and/or Sponsor also have the right to withdraw a subject from the study if it is no longer in the interest of the subject to continue in the study, or if the subject’s continuation in the study places the scientific outcome of the study at risk (eg, if a subject does not or cannot follow study

procedures). All subjects who are withdrawn from the study should complete protocol-specified early discontinuation procedures (Section 4.2.2.2).

4.2.2.1. Reasons for Withdrawal/Early Discontinuation

A subject may decide to withdraw from the study at any time, for any reason, without prejudice to subsequent care or treatment by the Investigator. When this occurs, the subject should complete all the procedures for the Week 52 (EOT) Visit. Subjects who discontinue the treatment due to AEs should remain under observation until the resolution or stabilization of the AEs. A subject may be discontinued from the study drug treatment before completion for any of the following reasons:

1. Subject death
2. Subject experiences an AE(s)/SAE(s) that warrants discontinuation, as judged by the Investigator and/or Insmed Medical Director
3. A major protocol deviation, which, in the opinion/discretion of the Investigator and/or Insmed, compromises the data integrity of the study
4. Subject is noncompliant with the study drug treatment (defined as <80% compliance after at least 2 reeducation efforts)
5. Withdrawal by subject
6. Termination of the study by the Sponsor
7. Investigator discretion
8. Subject lost to follow-up
9. Subject pregnancy
10. Periodontal criteria met (see Section 9.10.3.2)
11. Skin criteria met (see Section 9.10.3.1)
12. Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
13. Serious infection, defined as any infection other than associated with a pulmonary exacerbation that:
    a. Requires parenteral treatment with an antibiotic requiring admission to the hospital, or parenteral treatment with an antifungal, antiviral, antiparasitic, or antiprotozoal agent
    b. Is opportunistic, such as TB or other infections whose nature or course may suggest an immunocompromised status
14. Subjects who develop neutropenia defined as ANC <1000/mm^3
15. Subjects who have the following:
    a. ALT and/or AST values >3 × ULN and total bilirubin >2 × ULN, excluding confirmed Gilbert's Syndrome
    b. Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks).

Except for those subjects who withdraw consent, die, or are lost to follow-up, subjects who discontinue their assigned study drug will be encouraged to continue to participate in their remaining scheduled study visits. Every effort should be made by the Investigator to keep these subjects in the study through Visit 11. "Lost to follow-up" should be marked only in an exceptional case when all documented attempts to reach the subject by the Investigator or other staff members were unsuccessful.

4.2.2.2. Early Discontinuation Procedures

If a subject prematurely discontinues the study, the subject will have:

- An EOT Visit; however, the Investigator should contact the medical monitor to determine if the EOT CT assessment will be needed for subjects in the CT scan substudy.

If a subject withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reasons for withdrawal.

If the subject is discontinued from the study due to an AE, the Investigator will follow the subject as described in Section 9.10 and Section 9.12 .

4.2.2.3. Lost to Follow-up

A subject will be considered lost to follow-up from the study if the site is unable to contact the subject after 3 reasonable efforts have been made and a certified letter has been sent to subject/family.

4.2.3. Subject Replacement

Subjects who prematurely discontinue from the study after randomization will not be replaced, except for those who are replaced due to the war in Ukraine as agreed with FDA and EMA.

4.2.4. Subject Rescreening Procedures

Subjects who meet all inclusion criteria but fail Screening due to active PE, adjustment of Baseline medications within 1 month prior to Screening, or use of chronic oral or inhaled antibiotics for NCFBE ≤3 months prior to Screening can be rescreened up to 2 times with the Sponsor's Medical Director approval. Subjects who are undergoing standard dental care may be enrolled if the dental care is not related to periodontal disease and after consultation with the Medical Director. If a subject is approved for rescreening, the Medical Director will determine if some or all Screening assessments must be repeated. Rescreened subjects will be assigned a new Subject Number by the IWRS system.

4.3. Premature Termination of the Study

The Investigator may terminate a subject's participation in the study prematurely at their own discretion; if this occurs, the Investigator must contact the Sponsor immediately. The Sponsor may decide to terminate the participation of a site in the study or decide to terminate the study prematurely; if this occurs, written notification of the study termination is required to be sent to the site.

Conditions that may warrant study termination may include the following:

- Discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the Investigator to enter study subjects at an acceptable rate
- Insufficient adherence to protocol requirements (eg, noncompliance) by the subject and/or the study site
- Decision on the part of the Sponsor to suspend or discontinue development of the drug
- Decision by a regulatory authority or the Sponsor to stop the study at any time, where applicable

In the event of study discontinuation, subjects will discontinue study treatment. Refer to Section 4.2.2.2 for early discontinuation procedures.

The Sponsor will notify the regulatory authorities in all countries where the study is being conducted regarding the reason for terminating the study.

5. STUDY TREATMENT

The Investigator must ensure that the study treatment will be used only in accordance with the protocol.

5.1. Study Treatments Administered

5.1.1. Brensocatib

Brensocatib oral tablets have been developed for clinical studies and will be available for this study in strengths of 10- and 25-mg. The 2 strengths are round, biconvex, brown film-coated tablets, identical in size and appearance. The tablets are an immediate-release dosage form.

Each tablet contains the active ingredient brensocatib drug substance and the following inactive United States Pharmacopoeia/National Formulary or European Pharmacopoeia compendial ingredients: microcrystalline cellulose, dibasic calcium phosphate dihydrate, sodium starch glycolate, silicon dioxide, and glyceryl behenate. The film-coating system consists of polyvinyl alcohol, polyethylene glycol, titanium dioxide, iron oxide red, iron oxide yellow, iron oxide black, and talc.

In the current study, brensocatib oral tablets of 10- and 25-mg will be supplied to subjects based on treatment assignment.

5.1.2. Placebo

The matching placebo without the active ingredient is a film-coated tablet identical to brensocatib film-coated tablets in shape, size, and color.

In the current study, placebo film-coated tablets, identical in appearance to brensocatib 10- and 25-mg tablets will be supplied to subjects based on treatment assignment.

5.2. Methods of Assigning Subjects to Treatment

After meeting all inclusion criteria and none of the exclusion criteria, adult subjects will be randomized through an IWRS in a 1:1:1 ratio to 1 of the 3 treatment groups: brensocatib 10 mg, brensocatib 25 mg, or matching placebo (approximately 540 subjects per treatment arm). Randomization will be stratified based on a geographic region (North America, Europe, Japan, and the Rest of the World), sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, and the number of prior PEs (2, or ≥3) in the previous 12 months.

Randomization will be enforced to have approximately 30% of adult subjects with 3 or more prior PEs, to have no more than 20% of subjects older than 75 years of age, to have approximately no more than 20% of subjects with eosinophil count in peripheral blood ≥300/mm^3 at Screening, and to have no more than 20% of subjects with COPD as a comorbidity. Additionally, enrollment targets have been established for adult subjects with up to 13% of subjects from Eastern Europe and with North America, Western Europe, Asia Pacific, and Latin America contributing between 20% and 30% each. No single country (except the US) will contribute more than 15% of the overall randomized population.

Approximately 40 adolescent subjects will be randomized through an IWRS in a 2:2:1 ratio to 1 of 3 treatment groups: brensocatib 10 mg, brensocatib 25 mg, or matching placebo (approximately 16:16:8 subjects per treatment arm, respectively). Adolescent subjects will not be required to produce a sputum sample at the Screening Visit if they are unable. There will be no stratification for adolescent subjects.

Investigators (including independent evaluator/raters and clinicians providing care to the subject), Sponsor, and subjects/caregivers will be blinded to treatment group assignments throughout the study.

Study personnel and subjects are strongly discouraged from discussing any aspect of study treatment, with the exception of safety issues, in order to maintain treatment blinding and study integrity.

Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review (Section 3.2).

Unblinding is only to occur in the case of subject emergencies (Section 5.6) and at the conclusion of the study.

5.3. Study Treatment Administration

Brensocatib 10 mg, brensocatib 25 mg, or placebo will be administered QD by mouth with water in the morning before breakfast; tablets must not be broken or chewed. Subjects will be instructed to record each daily dose of study drug administered in an electronic dosing diary. On the days of clinical study visits, including Visit 11 (Week 52), study drug will be administered at the study site by study personnel after collection of all applicable patient-reported outcome measures (Section 7.5) and after sputum collection (Table 5).

5.4. Dose Interruption

The Investigator may interrupt dosing for safety reasons.

5.5. Method of Assessing Treatment Compliance

Subjects will be required to bring all their used and unused study drug bottles as well as their electronic dosing diary to each in-clinic study visit during the treatment period.

Accountability for study drugs administration during the study is the responsibility of the Investigator or designees. Drug accountability will be recorded at each in-clinic study visit by review of eCRF data and count of returned study drugs.

A subject will be considered noncompliant with study drugs if treatment adherence is less than 75% or more than 120% unless instructed by the Investigator to interrupt dosing for safety reasons (Section 5.4). Subjects who are noncompliant with study drug should be retrained. Continued noncompliance may result in premature discontinuation of study treatment (Section 4.2).

5.6. Emergency Unblinding

Unblinding of treatment assignment for a subject may be necessary due to a medical emergency, or any other significant medical event (eg, pregnancy).

In the case of a rare emergency where, in the opinion of the Investigator, discontinuation of study treatment is not sufficient, and the study treatment must be unblinded to evaluate further course of action, the Investigator can unblind study treatment for a specific subject. After unblinding, it is suggested that the Investigator contact the Insmed Medical Monitor or appropriate Insmed study personnel to inform of the unblinding. The Investigator must be able to confirm that unblinding of the subject is necessary and directly impacts the subject's immediate medical management or welfare of the subject. The subject will be considered discontinued from the study.

The Investigator must notify the Sponsor of the unblinding as soon as possible. The date and reason for unblinding must be documented in the source documents and signed by the study Investigator. The originally signed copy (eg, Note to File) is maintained in the study file at the site, and a copy is provided to the Sponsor or its designee. The Investigator should follow the steps in the IWRS system and enter the unblinding date.

5.7. Labeling and Packaging

Subjects will receive bottles containing tablets of brensocatib 10 mg, brensocatib 25 mg, or placebo.

Labels will be prepared in accordance with GMP requirements and local regulatory guidelines. Label text will be translated into local language(s).

5.8. Storage

Study drug will be shipped to the study site after the first subject is screened. Brensocatib must be stored between 2°C and 30°C (36°F to 86°F). Do not freeze.

At the study site, all study drugs must be stored in a secured, environmentally controlled, and monitored location with restricted access in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Refer to the pharmacy manual for more detailed information on shelf-life and storage conditions.

5.9. Dispensing of Study Drug

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply, prepare, or administer study treatment. The IWRS system will be used to track and record the dispensing of study treatments throughout the study.

At each in-clinic visit, subjects will be dispensed adequate study drugs to allow for daily dosing, including extra supply for potential study visit scheduling delays. Study drug may be dispensed directly to the subject's home by courier if dispensing at the site is not feasible.

5.10. Drug Accountability

Drug accountability records will be maintained for all clinical supplies. All transactions will be recorded on the drug accountability records including shipment receipts and study subject doses. All transactions will be recorded on a real-time basis.

The pharmacy will maintain detailed documentation of the number and identification of bottles and dispensing units with copies of these documents to be provided to the Sponsor at the end of the study. Study drug accountability should follow institutional SOP, or a plan agreeable by Insmed, including appropriate actions during monitoring visits or other form of drug accountability monitoring through remote methods. Upon completion of the drug inventory by the study monitor, used and any unused vials and tablets will be disposed of in accordance with instructions provided to sites and according to site destruction policies. The drug may be destroyed at site per site SOP or returned to the local drug depot in the case that destruction is not possible. Study treatment that is returned to the local drug depot must be documented in the accountability documentation. Documentation of destruction should be provided to the Sponsor

5.11. Concomitant Medications

Any medications the subject takes other than the study drugs, including all vaccinations received, from Visit 2 (Baseline, Day 1) to Visit 12 (EOS, Week 56) are considered concomitant medications and will be collected and documented in the study eCRF.

Prior medications are those medications taken before the first dose of study drug. Concomitant medications are those medications taken after the first dose of study drug. A medication that starts prior to first dose but continues after the first dose of study drug is classified both in prior and concomitant medications. Any procedures performed, including all diagnostic tests, from Visit 2 (Baseline, Day 1) to Visit 12 (EOS, Week 56) are considered concomitant procedures and will be collected and documented in the study eCRF.

5.11.1. Prohibited Medications and Procedures

Prohibited medications are as follows:

- Use of any immunomodulatory agents within 4 weeks before the Screening Visit (including but not limited to: bortezomib, ixazomib, thalidomide, cyclophosphamide, mycophenolate, Janus kinase inhibitors, IFN-γ, and azathioprine) is prohibited during the study through Visit 12 (EOS)
- Continuous use of high dose non-steroidal anti-inflammatory drugs is prohibited during the study through Visit 12 (EOS) (see Appendix 7, Comparable NSAID Dose Levels)
- Chronic treatment with systemic steroids (irrespective of the indication) is prohibited Note: Chronic treatment is considered >14 days of continuous use
- Live attenuated vaccines are prohibited during the study (until 4 weeks after the last dose of study drug)
- Use of investigational drugs within 3 months of the Screening Visit

The following procedures are prohibited during study participation:

- Major elective surgical procedures
- Elective periodontal procedures

Subjects who have already scheduled a major surgical procedure or who have a prescheduled periodontal procedure are not eligible to participate in the study.

5.11.2. Permitted Medications and Procedures

Any concurrent ongoing medications, including over-the-counter drugs are allowed if not prohibited by the protocol (see Section 5.11.1).

Subjects should continue their maintenance doses of oral or inhaled antibiotics or inhaled corticosteroids during the study. Subjects can use LABA, LAMA, anticholinergic bronchodilators, PDE4 inhibitors, and their reliever medication (SABA, SAMA) during the study if prescribed by their physicians. Subjects are also allowed to continue their airway clearance maintenance treatment/procedures such as use of hypertonic saline/isotonic saline, mucolytics, and pulmonary rehabilitation. However, except under unforeseeable clinical circumstances, the airway clearance maintenance treatment/procedures and pulmonary rehabilitation should continue unchanged throughout the duration of the study through Visit 12 (EOS).

There is a minimum time interval restriction for some of the medication use before and after spirometry testing. The minimum time intervals of the restricted medications are summarized in Table 4.

Table 4: Minimum Time Intervals for Restricted Medication Use Prior to Spirometry Testing

Medication	Minimal Time Interval From Last Medication Dose Prior to Spirometry Testing
Inhaled SABA (Salbutamol/Albuterol, Terbutaline)	6 Hours
Inhaled LABA, Including ICS/LABA Combination Products	
Formoterol	12 Hours
Salmeterol	12 Hours
Olodaterol	24 Hours
Indacaterol	24 Hours
Oral β_2-Agonists:	
Short-Acting	6 Hours
Long-Acting	24 Hours
Transdermal β_2-Agonists	24 Hours
Inhaled SAMA (ipratropium bromide)	6 Hours
Inhaled LAMA, Including LAMA/LABA and ICS/LAMA Combination Products	
Aclidinium	12 Hours
Tiotropium	24 Hours

Medication	Minimal Time Interval From Last Medication Dose Prior to Spirometry Testing
Glycopyrrolate	24 Hours
Umeclidinium	24 Hours
Xanthines	
Twice Daily	12 Hours
Once Daily	24 Hours
Roflumilast	24 Hours
Ephedrine -Containing Drugs	6 Hours
Leukotriene Receptor Antagonists	Allowed

ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist.

5.11.3. Rescue Therapy

Not applicable.

6. STUDY PROCEDURES

6.1. Schedule of Assessments

The Schedule of Assessments and Procedures is presented in Table 5.

Table 5: Schedule of Assessments and Procedures

Study Period	Screen	Treatment Period										Follow-Up
Study Days Study Weeks	**Days -42 to -1**	**D1 (Baseline)**	**D28 Wk4**	**D70 Wk10**	**D112 Wk16**	**D154 Wk22**	**D196 Wk28**	**D238 Wk34**	**D280 Wk40**	**D322 Wk46**	**D364 Wk52 (EOT or E/D)[a]**	**D392 Wk56 (EOS)**
Visit	**V1**	**V2**	**V3**	**Phone V4[b]**	**V5**	**Phone V6[b]**	**V7**	**Phone V8[b]**	**V9**	**Phone V10[b]**	**V11**	**V12**
Obtain informed consent (and assent if required per local requirements for adolescent population)	X											
Demographics and medical history[c]	X	X[b]					`					
Smoking status	X	X	X	X	X	X	X	X	X	X	X	X
Height, weight, and BMI calculation[d]	X										X[d]	
Vital signs (BP, HR, T, RR, O2 saturation)[e]	X	X	X		X		X		X		X	X
Clinical laboratory tests (hematology, blood chemistry, and urinalysis) [e,f]	X	X	X		X		X		X		X	X
Physical examination	X										X	
PFT by spirometry (FEV_1, $ppFEV_1$, FVC, $FEF_{[25-75\%]}$, PEFR)[g]	X	X			X		X		X		X	
Chest CT scan for eligibility[h]	X											
CT scan substudy[i]	X										X	
12-lead ECG[j]	X	X	X				X		X		X	
HBcAb, HBsAb, HBsAg, HIV, and HCV tests	X											
Serum/urine pregnancy test[k]	X	X	X	X	X	X	X	X	X	X	X	X
FSH level for WOCBP ≤45 years of age	X											

Study Period	**Screen**	**Treatment Period**										**Follow-Up**
Study Days **Study Weeks**	**Days -42 to -1**	**D1 (Baseline)**	**D28 Wk4**	**D70 Wk10**	**D112 Wk16**	**D154 Wk22**	**D196 Wk28**	**D238 Wk34**	**D280 Wk40**	**D322 Wk46**	**D364 Wk52 (EOT or E/D)[a]**	**D392 Wk56 (EOS)**
Visit	**V1**	**V2**	**V3**	**Phone V4[b]**	**V5**	**Phone V6[b]**	**V7**	**Phone V8[b]**	**V9**	**Phone V10[b]**	**V11**	**V12**
Estimated glomerular filtration rate calculation per CKD-EPI Formula	X				X		X				X	
Sputum sample collection for sputum color and *P aeruginosa* determination[l]	X											
Dental hygiene education[m]	X	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[n]		X										
Assess for pulmonary exacerbation		X	X	X	X	X	X	X	X	X	X	X
Bronchiectasis Severity Index calculation (by sites)		X										
BEST electronic subject diary completion[o]	----------Complete every day----------											
QOL-B completion and review[p]		X	----------Complete every 2 weeks ----------									
PGI-S[q]		X	----------Complete every 2 weeks ----------									
PGI-C[q]			----------Complete every 2 weeks ----------									
EQ-5D-5L/ QOL-PCD – Completion at site[r]		X	X		X		X		X		X	X
Blood PK samples[s]		X	X		X		X		X		X	
Sputum PD sample[t]	X	X	X		X		X		X		X	X
For substudy only: blood PD[u]	X	X	X		X		X		X		X	X
Health resource utilization[v]			X	X	X	X	X	X	X	X	X	

Study Period	Screen	Treatment Period										Follow-Up
Study Days Study Weeks	**Days -42 to -1**	**D1 (Baseline)**	**D28 Wk4**	**D70 Wk10**	**D112 Wk16**	**D154 Wk22**	**D196 Wk28**	**D238 Wk34**	**D280 Wk40**	**D322 Wk46**	**D364 Wk52 (EOT or E/D)[a]**	**D392 Wk56 (EOS)**
Visit	**V1**	**V2**	**V3**	**Phone V4[b]**	**V5**	**Phone V6[b]**	**V7**	**Phone V8[b]**	**V9**	**Phone V10[b]**	**V11**	**V12**
Collect days of work/ school missed			X	X	X	X	X	X	X	X	X	
Dispense study drug, accountability of returned drug, and review of dosing diary[w]		X	X		X		X		X		X[w]	X[w]
Adverse events collection		X	X	X	X	X	X	X	X	X	X	X
Assessment of skin conditions (hyperkeratosis of palm and soles)[x]		X	X		X		X		X		X	X
Assessment of periodontitis[y]		X	X	X	X	X	X	X	X	X	X	X

Note: for each of the Study Visits from Visit 3 to End of Study (Visit 12), there is a ±7-day window.

[a] Visit 11 (Week 52) is completed for those who finish study treatment per protocol. The visit is alternatively completed for those who discontinue early from study treatment.

[b] For Phone Visits, collect data outlined in Phone Visit Sheet: exacerbations, safety events, hospitalizations, or emergency room visits (including start and end date, follow-up with facility to retrieve source documentation), days of work missed (including start and end date), IV antibacterial drug use (including start and end dates), list of new rescue medications (including name, and start and end dates).

[c] Demographics and medical history: At Visit 2 (Baseline) only medical history collected.

[d] Height, weight, and BMI: Body weight will be measured at Screening and at the Week 52 (Visit 11; EOT). For adult subjects, the measurement of height, without shoes, will be performed at Screening Visit only. For adolescent subjects, measurement of height, without shoes, will be performed at Screening Visit and Visit 11 (EOT).

[e] Vital signs and clinical laboratory blood samples will be collected at the Screening Visit and prior to the first dose of the study drug on Day 1 (Baseline), and at every in-clinic visit. Vital signs include the following: systolic and diastolic blood pressure, respiratory rate (breaths per minute), pulse (beats per minute), body temperature (°C), and oxygen saturation. Clinical laboratory parameters are listed in Table 6.

[f] Clinical laboratory blood samples should be collected in a fasted state (after an overnight fast for morning sample collection or at least 4 hours without food at other times) if possible.

[g] Spirometry will be performed preferably in the morning (at the same time of day each time) and performed after withholding the last dose of SABA for 6 hours, or LABA for 12 hours or LAMA for 24 hours or ultra-long LABA for 24 hours.

[h] Perform high-resolution chest CT scan at the Screening Visit if subject does not have prior radiological confirmation of NCFBE diagnosis or CT scan is older than 5 years from date of the Screening Visit or the existing CT scan cannot be read due to quality issues.

[i] For the CT scan substudy (n=approximately 225 adult subjects), a new high-resolution CT scan must be performed during the Screening Period and at the Week 52 Visit. The Investigator should contact the medical monitor for any patient who prematurely discontinues from the study to determine if the EOT assessment is needed.

[j] It is recommended to obtain the 12-lead ECG before PFT by spirometry when scheduled at the same visit.

[k] Serum and urine pregnancy tests will be performed for WOCBP. A serum pregnancy test will be performed at the Screening Visit; a urine pregnancy test for WOCBP including adolescent female subjects will be performed at Baseline (Day 1) and all other visits. In addition to the pregnancy tests required by the Schedule of Assessments, monthly urine pregnancy tests should be performed by WOCBP in countries where it is required by local health authority. During the treatment period, adolescent female subjects who have reached menarche will perform a urine pregnancy test at all clinical visits (and monthly where required by local health authority). Please note that on days of Phone Visits, WOCBP will be provided with urine pregnancy kits; the test should be performed at home on the day of the Phone Visit, and the results reported during the Phone Visits.

[l] All subjects will provide sputum at Screening for a microbiology culture for *Pseudomonas aeruginosa* and color evaluation. The result will be reviewed at Baseline and used for randomization stratification. A subject should not undergo a sputum induction procedure during the Screening Visit (Visit 1) to meet the inclusion criterion. Adolescent subjects are exempt from requirement to provide a sputum sample if they are unable to do so.

[m] Dental hygiene education includes instructions on daily teeth brushing and flossing.

[n] Randomization: Eligibility should be reassessed prior to randomization at Visit 2 (Baseline). Subjects who do not meet all inclusion/exclusion criteria will NOT be randomized and will be considered a screen failure. However, subjects who meet all inclusion criteria but fail Screening due to active pulmonary exacerbation, adjustment of Baseline medications within 1 month prior to Screening, or use of oral or inhaled antibiotics for NCFBE ≤3 months prior to Screening Visit can be rescreened up to 2 times upon Sponsor (Medical Director) approval. Subjects who are undergoing standard dental care may be enrolled if the dental care is not related to periodontal disease and after consultation with the Medical Director. If a subject is approved for rescreening, the Medical Director will determine if some or all Screening assessments must be repeated. Rescreened subjects will be assigned a new Subject Number within the IWRS system.

[o] BEST questionnaire: Adult subjects should complete the BEST questionnaire (in the evening) on an electronic diary DAILY from the Screening Visit through EOS Visit (Week 56). If there is an increase of symptoms (as per the algorithm programmed in the electronic data capture system) the site and the subject will be alerted. The subject will be asked to contact the site within 1 business day and the site will receive a message to contact the subject within 1 business day. The goal is to assess if a pulmonary exacerbation or any other medically relevant event is taking place. Subjects should be trained on completion of the questionnaires at Visit 1 (Screening). Subjects should be retrained if the compliance falls below 75% between each on-site visit after randomization.

[p] QOL-B: where validated translations are available in the local language, all adult subjects will complete the QOL-B on an electronic diary on Day 1 (Baseline) and every 2 weeks thereafter through Week 56. The QOL-B is considered “modified” because the first page, which only collects demographics information, will be deleted from the questionnaire since demographics are collected on the appropriate eCRF page instead.

[q] PGI-S and PGI-C: Newly enrolled adult subjects will complete the PGI-S and PGI-C on an electronic device where validated translations are available in the local language. Existing subjects will not complete the PGI-S and PGI-C.

[r] EQ-5D-5L: All subjects (adult and adolescent) will complete the EQ-5D-5L at the site on an electronic device at Visit 2 (Baseline), and at every scheduled in-clinic visit. Where validated translations are available in the local language, adolescent subjects with PCD will complete the age-appropriate QOL-PCD. The questionnaires should be reviewed by the Investigator during each visit. Subjects should be trained before administration of the first dose of their assigned study drug on Visit 2 (Day 1). Subjects will be retrained on how to complete the questionnaires correctly if needed.

[s] Blood PK samples: Predose blood PK samples will be collected from all subjects at the designated visits, with an optional 2-hour (±30 minutes) postdose sample collected at select visits (ie, Day 1, Week 4, Week 28, and Week 40) (Appendix 5). Approximately 300 adult subjects and 40 adolescent subjects who are not receiving cyclic antibiotics at Baseline from selected sites will participate in the PK substudy in which blood PK samples will be collected at the same designated visits, with collections at additional timepoints as indicated in Appendix 5.

[t] Sputum PD samples: At designated study visits, predose sputum PD samples will be collected from all newly enrolled subjects and from subjects participating in the PK/PD substudy who are not receiving cyclic antibiotics at Baseline (see Appendix 6). Approximately 3 mL of sputum will be collected at each timepoint. Sputum induction is allowed only after the Screening Visit. Adolescent subjects are exempt from providing a sputum sample at the Screening Visit if they are unable to provide.

[u] Blood PD samples: Of the approximately 300 adult subjects participating in the PK/PD substudy who are not receiving cyclic antibiotics at Baseline, approximately 40 subjects at selected sites will participate in the blood PD substudy. Blood samples will be collected at the Screening Visit, at 0 (predose) on Day 1, at predose at Week 4, Week 16, Week 28, Week 40, Week 52, and at Week 56 (follow-up) (see Appendix 6).

[v] Health Resource Utilization: Collect healthcare visit information such as the type of visit (hospitalization, doctor, or ER), reason for visit, and visit date.

[w] On study visit days, study drug will be administered at the study site by study personnel after collection of available PRO instruments and after sputum collection. Study drug is not dispensed at the Week 52 or the Week 56 visits.

[x] Skin examination, especially palms and soles, dorsum of the hands and feet, Achilles tendon area, knees, and elbows, will be performed by the Investigator at each in-clinic visit. If there are any signs or symptoms of hyperkeratosis or erythema or deterioration of the pre-existing conditions that warrant further evaluation upon Investigator discretion, the subject will be referred to a dermatologist for further assessment. The skin evaluation by the dermatologist for the subject should then be assessed thereafter on an interval per the dermatologist discretion until end of the study.

[y] Questions about the presence of any periodontal complaint will be asked at every visit (including telephone visits). For adolescents, an oral and dental inspection for any signs or symptoms of gingivitis or periodontitis will be performed by the Investigator at each visit. If there are any signs or symptoms of gingivitis or periodontitis that warrant further evaluation upon Investigator discretion, the subject will be referred to a dentist for further assessment. The oral and dental evaluation by the dentist for the subject should then be assessed thereafter on an interval per the dentist's discretion until the EOS Visit.

BEST=Bronchiectasis Exacerbation and Symptoms Tool, BMI=body mass index, BP=blood pressure, CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration, CT=computed tomography, ECG=electrocardiogram, eCRF=electronic case report form, E/D=Early Discontinuation; EOS=End of Study, EOT=End of Treatment, EQ-5D-5L=EuroQoL-5 Dimension-5 Level Questionnaire, FVC=forced vital capacity, $FEF_{25-75\%}$=forced expiratory flow between 25% and 75% of forced vital capacity, FEV_1=forced expiratory volume in 1 second, FSH=follicle-stimulating hormone, HBcAb=hepatitis B core antibody, HBsAb=hepatitis B surface antibody, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=heart rate, IV=intravenous, IWRS=interactive web response system, NCFBE=non-cystic fibrosis bronchiectasis, PD=pharmacodynamic, PEFR=peak expiratory flow rate, PGI-C=Patient Global Impression of Change scale, PGI-S=Patient Global Impression of Severity scale, PFT=pulmonary function test(s), PK=pharmacokinetic, $ppFEV_1$=percent predicted forced expiratory volume in 1 second, PRO=patient report outcomes, QoL-B=Quality of Life Questionnaire – Bronchiectasis, QOL-PCD=Quality of Life Questionnaire – Primary Ciliary Dyskinesia, RR=respiration rate, T=temperature, WOCBP=women of childbearing potential.

6.2. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol as agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

As of May 2020, due to concern regarding COVID-19, there may be restrictions to subject attendance at in-clinic visits. In the event subjects are restricted to attend in-clinic visits, or if the subject has concern regarding travel and attending in-clinic visits (due to potential public health concerns), the site should contact the Sponsor on how to conduct the scheduled assessments, and decisions should be documented in the source documentation. Where necessary, in-clinic visits may be conducted via telemedicine link and home health care visits.

6.3. Public Health Emergency Situations

During the COVID-19 public health emergency, the Sponsor, IRB/IECs, and Investigators shall follow the most current version of local guidance to assure the safety of study subjects, maintain compliance with GCP, and minimize risks to study integrity. In anticipation that the COVID-19 pandemic may have an impact on the conduct of clinical studies, the Sponsor does not intend to screen any new subjects in this study unless the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of the study at individual sites, and subjects can safely participate in this study. The continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, which will remain in effect only for the duration of the local public health emergency. Examples of such mechanisms may include, but are not limited to, any of the following: telephone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. The site should contact the Sponsor on how and when to implement temporary and/or alternative mechanism of scheduled assessments, and all decisions taken should be documented in the source documentation. Additionally, all temporary mechanisms utilized, and the resulting deviations from planned study procedures are to be documented as being related to COVID-19.

In a situation where local health authorities declare a public health emergency while the trial is ongoing, the suggested guidance in the following subsections should be followed.

6.3.1. Continuation or Suspension of the Study

Ensuring the safety of trial participants is paramount. The Sponsor (Insmed Incorporated), in consultation with clinical Investigators and IRB/IEC, will determine if the protection of a participant’s safety, welfare, and rights are best served by continuing or stopping the trial at the specific site. Such decision will depend on specific circumstances, including the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and other considerations.

If the decision is to continue the study, the following considerations will be taken into account.

6.3.1.1. Study Recruitment

The Sponsor will communicate to the sites the decision on whether to continue or suspend recruitment after considering the specific circumstances of each site, recommendation by the IRB/EC, and its local health authority mandates. If, due to COVID-19, study discontinuation exceeds the assumed rate, the Sponsor may allow enrollment past the assumed sample size.

6.3.1.2. Subjects Already Enrolled in the Study

If the decision is to continue the participation of subjects already enrolled, the following steps should be taken:

- If a subject is not able to complete a protocol-specified study visit, it may be necessary to adjust the visit schedule, convert in-clinic visits to telemedicine visits, and/or postpone study procedures until the next available in-clinic study visit. If there is information available from previous visits (ie, laboratory assessments) that requires follow-up procedures or other safety assessments, the Investigator will decide if an on-site visit or home healthcare visit is required or whether the subject's safety can be preserved by other means
- If study participants no longer have access to investigational product, specific procedures should be put in place to ensure delivery of investigational product to subject provided all safety considerations and applicable health authority requirements have been addressed.

6.3.2. Subjects Infected by COVID-19

If a subject has had a past documented infection by COVID-19 prior to enrollment in the trial but the subject has recovered and the current diagnostic tests are negative (negative antigen by any diagnostic laboratory kit), the subject can be rescreened if the disease (COVID-19) was mild or moderate, excluding those subjects who experienced hospitalization, severe disease, and/or COVID-19 ARDS.

If a subject has a documented infection by COVID-19 while in the trial:

- The event will be reported as an AE or SAE, depending on the criteria.

The site will follow the guidance provided by health authorities in the treatment of those subjects.

7. EFFICACY ASSESSMENTS

7.1. Pulmonary Exacerbation

A *pulmonary exacerbation* is defined by having ≥3 of the following symptoms for at least 48 hours, resulting in a physician's decision to prescribe systemic antibiotics:

- Increased cough
- Increased sputum volume or change in sputum consistency
- Increased sputum purulence
- Increased breathlessness and/or decreased exercise tolerance
- Fatigue and/or malaise
- Hemoptysis

Note: Subjects on chronic macrolide therapy whose only change in therapy is dose or frequency adjustment will not meet the definition of PE.

A *severe pulmonary exacerbation* is defined as those requiring IV antibacterial drug treatment and/or hospitalization.

Any pulmonary exacerbation in the study after randomization through the end of the 52-week treatment period will be included in the primary endpoint calculation (provided it meets the protocol-defined criteria). A minimum of 14 days must occur between the end date of one pulmonary exacerbation and the start date of the next pulmonary exacerbation. Any exacerbations that occur less than 14 days from the prior exacerbation will not be considered a new exacerbation.

The time to the first pulmonary exacerbation is calculated from the randomization date to the onset date of the first exacerbation. Subjects who do not have an exacerbation at the end of the 52-week treatment period will be censored at the date of Week 52. Subjects who have ≥1 PE during the study will have event counts and corresponding time to event calculations.

7.2. Sputum

7.2.1. Sputum Culture

All patients will provide a sputum sample at the Screening Visit to assess the color of the sample and whether *P aeruginosa* is present, for stratification purposes. Adolescent subjects are exempt from the requirement to produce a sputum sample at Screening if they are unable to do so.

Detailed instructions for collecting, processing, and shipping sputum specimens will be provided in the site laboratory manual.

7.2.2. Sputum for PK/PD Substudy

The PK/PD substudy will include subjects who are not receiving cyclic antibiotics at Baseline. Adult subjects enrolled in the PK/PD substudy and adolescent subjects who are able to do so will provide a sputum sample at Screening (sputum induction procedure is not allowed at Screening).

The sample will be sent to the PK/PD laboratory to assess the presence of NSPs (NE, CatG and PR3).

Predose expectorated or induced sputum specimens (approximately 3 mL) are collected from adult and adolescent subjects at each clinic visit as specified in the Schedule of Assessments (Table 5). If a subject is unable to produce sputum spontaneously, sputum may be induced as suggested in Appendix 1, if these suggestions are safe for the subject. If after induction, a subject is still unable to produce sputum despite reasonable efforts, and the site does not consider any alternative for obtaining the sputum sample, this will be recorded as non-productive at that time point. At the scheduled visit, once sputum is collected (spontaneously or by induction), study drug can be administered.

Detailed instructions for collecting, processing, and shipping sputum specimens will be provided in the site laboratory manual.

7.3. Pulmonary Function Tests

Pulmonary function tests include the following: pre- and postbronchodilator FEV_1, pre- and postbronchodilator $ppFEV_1$, FVC, $FEF_{(25-75\%)}$, and PEFR.

Pre- and postbronchodilator PFT by spirometry (FEV_1, $ppFEV_1$, FVC, PEFR, and $FEF_{[25-75\%]}$) will be performed per the ATS/ERS criteria (Miller et al., 2005) at Visit 1 (Screening), Visit 2 (Baseline), Visit 5 (Week 16), Visit 7 (Week 28), Visit 9 (Week 40), and Visit 11 (Week 52) (Table 5). Subjects should be provided with detailed instruction on how to conduct the FVC maneuver per ATS/ERS spirometry standardization before performing the test.

Subjects should be advised to withhold short-acting inhaled drugs (eg, the β-agonist albuterol/salbutamol or the anticholinergic agent ipratropium bromide) within 6 hours prior to the test. Long-acting β-agonist bronchodilators (eg, salmeterol or formoterol) or long-acting muscarinic bronchodilators (eg, tiotropium) or oral therapy with aminophylline or slow release β-agonists should be withheld for 12 to 24 hours depending on the medication used (refer to Table 4 for the minimum time intervals for a list of restricted medications) prior to the testing.

In the event a subject has taken a restricted medication during the specified time interval before the test, the test should be rescheduled for another visit within the protocol-specified visit window. If rescheduling the visit is not feasible for the subject, the test should be conducted as usual with appropriate notation in the source documents.

Spirometry should be performed preferably in the morning (AM) at approximately the same time each visit. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements. Pulmonary function tests will be measured in the sitting position; however, if necessary, to undertake the testing with the subject standing or in another position, this should be noted on the spirometry report. For any subject, the position should be consistent throughout the study. Three (3) measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable maneuvers, an explanation should be recorded in the eCRF. At least 2 acceptable curves must be obtained. The largest FEV_1 and largest FVC should be recorded after the data are examined from all of the acceptable curves,

even if they do not come from the same curve. The $FEF_{(25-75\%)}$ should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV_1 (best test). Automated best efforts, which combine FEV_1 and FVC are not acceptable. The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a study subject is assessed and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

Subjects should be advised to rest at least 30 minutes, and not to eat a large meal for at least 2 hours prior to the test. If a subject is scheduled to have pulmonary rehabilitation on the day of their visit, they should be advised to have the PFT done before the rehabilitation on that day.

Postbronchodilator spirometry tests will be performed per the following instructions:

- When an inhaled SABA is used, 4 puffs of albuterol/salbutamol, levalbuterol/levosalbutamol, or terbutaline will be administered. A postbronchodilator PFT will be performed 15 to 30 minutes after the administration of albuterol or levalbuterol.
- When an inhaled SAMA is used, 4 puffs of ipratropium will be administered. A postbronchodilator PFT will be performed within 20 to 30 minutes after the administration of ipratropium.
- If a subject cannot perform an inhalation, the SABA or SAMA can be nebulized. Pulmonary function tests should be performed within 20 to 30 minutes after finalization of nebulization.

NOTE: If a subject used SABA in the first assessment of PFTs, the same SABA and mode of administration should be used in subsequent assessments. If a subject used SAMA in the first assessment of PFTs, the SAMA and mode of administration should be used in subsequent assessments.

Detailed instructions on how to conduct the spirometry and document the results are provided in a separate spirometry manual.

7.4. Bronchiectasis Severity Index

The Bronchiectasis Severity Index (BSI) is a scoring system based on a combination of clinical, radiological and microbiological features that can be used to assess subjects' NCFBE severity. The BSI was validated in 1,310 subjects across 4 European bronchiectasis centers. The BSI has been shown to give excellent predictions of mortality and hospital admissions and be predictive of exacerbations and QOL giving a broad assessment of disease severity (Chalmers et al., 2014).

The BSI score will be calculated at Baseline and documented in the study source document and eCRF. Appendix 2 presents the methodology for the scoring of the BSI.

7.5. Patient-Reported Outcome Measures

7.5.1. Bronchiectasis Exacerbation and Symptoms Tool

Bronchiectasis Exacerbation and Symptom Tool (Artaraz et al., 2020) is a novel symptom diary for bronchiectasis symptom burden and detection of exacerbations, named the BEST diary. The BEST diary measures day-to-day changes in patient symptoms but also accurately detects exacerbations. The BEST symptom diary shows convergent validity with existing health questionnaires and is responsive at onset and recovery from exacerbation.

Adult subjects should complete the BEST symptom diary daily in the evening, from the Screening Visit through EOS Visit (Week 56). Subjects should be retrained if the compliance falls below 75% between each on-site visit after randomization. Compliance will be calculated by adding the number of days the questionnaire was completed divided by the number of days between on-site visits.

If there is an increase of symptoms (as per the algorithm programmed in the electronic data capture system) the site and the subject will be alerted. The subject will be asked to contact the site within 1 business day and the site will receive a message to contact the subject within 1 business day. The goal is to assess if a pulmonary exacerbation or any other medically relevant event is taking place. Subjects should be trained on completion of the questionnaire at Visit 1 (Screening).

7.5.2. Quality of Life Questionnaire – Bronchiectasis

The QOL-B is a validated, self-administered PRO that assesses symptoms, functioning, and health-related quality of life for subjects with NCFBE (Quittner et al., 2015). The QOL-B contains 37 items in 8 domains (Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions and Treatment Burden).

The QOL-B page 1 (demographics page) will be removed as demographics are collected on a separate eCRF page. The modified QOL-B, where validated translations are available in the local language, will be provided to all adult subjects in an electronic format on an electronic diary after randomization. Subjects will be required to complete the QOL-B after the training and prior to the administration of the first dose of their assigned study drug at Visit 2 (Day 1; Baseline). Subjects will complete the questionnaire directly on the electronic diary every 2 weeks from Day 1 to Week 56 (Table 5).

The subjects will complete the questionnaire while they are in the clinic if the study visit coincides with the availability of the questionnaire (in validated translation of the local language) and at home for the weeks in between the study visits. It is important for the site staff to remind the subjects to bring their electronic diaries with them to each clinic visit.

On days when the subject is at home (ie, days without study center visits), patient-reported outcome assessments are to be completed when they become available on the electronic diary.

The completed questionnaires will be reviewed during each visit. Subjects will be retrained on how to complete the questionnaires correctly, if needed. For adults, the Respiratory Symptoms Domain score of the QOL-B will be assessed as a secondary endpoint, with the other domain scores of the QOL-B assessed as exploratory endpoints.

7.5.3. PGI-S and PGI-C

The PGI-S and the PGI-C scales will be used to assess the subject's overall perception of the severity and change in NCFBE status. These scales are intended to confirm a meaningful change threshold for the QOL-B Respiratory Symptoms Domain endpoint (Guy, 1976). The PGI-S and PGI-C are both 1-item questionnaires using balanced Likert scales that ask the subject to rate the severity of NCFBE (PGI-S, a single-state 5-point categorical scale) or to rate at a particular time point the perceived change in NCFBE status in response to treatment (PGI-C, a transitional 7-point categorical scale).

All newly enrolled adult subjects will complete the PGI-S and PGI-C at the time points indicated in Table 5 where translations are available in the local language (existing subjects will not complete either questionnaire). Subjects will be trained on how to complete the questionnaires using an electronic diary. The questionnaires will be completed in the clinic on clinic visit days and at home when completion is scheduled between clinic visits.

7.5.4. EuroQoL-5D-5L

The EuroQoL-5D-5L (EQ-5D-5L) is a 2-page instrument suitable for use in subjects ages 12 years and older with 2 components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (Herdman et al., 2011). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain evaluates severity on a 5-level scale: having no problems, having slight problems, having moderate problems, having severe problems, and being unable to do/having extreme problems. The EQ-5D-5L questionnaire VAS component allows respondents to report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status). All subjects (adult and adolescent) will complete the EQ-5D-5L at the site on an electronic device at the time points indicated in Table 5.

7.5.5. QOL-PCD

QOL-PCD is a specific quality of life questionnaire for patients with PCD. The questionnaire was developed using the most recent guidance from FDA and EMA and has undergone cognitive testing in pediatric patients from several English-speaking countries. The questionnaire will be completed by adolescent subjects in whom PCD is the cause of NCFBE and where a validated translation is available in the local language. The QOL-PCD questionnaire has 4 age-specific versions (adults ≥18 years, adolescents 13-17 years, children 6-12 years and a parent-proxy questionnaire for children 6-12 years). Age-appropriate versions of the QOL-PCD (at the time of randomization) will be used in the trial for all adolescent subjects. The questionnaire has 9 subscales in the 13-17 years of age group: Physical Functioning (n=5), Vitality (n=3), Emotional Functioning (n=5), Treatment Burden (n=4), Upper Respiratory Symptoms (n=4), Lower Respiratory Symptoms (n=6), Role (n=4), Social Functioning (n=3), Hearing Symptoms (n=2). Higher scores in each subscale represent increased health-related quality of life (Dell et al., 2016).

7.6. Chest CT Scan

At the Screening Visit, a chest CT scan image(s) for all subjects will be sent to the central reader for advanced centralized image analysis to evaluate if the NCFBE meets the enrollment criteria.

Only after this evaluation has been done and the CT scan has been read by the reviewers, can the subject be enrolled in the trial.

For each subject, the most recent chest CT (taken within 5 years of the Screening Visit) will be collected for centralized scoring by an independent Core Laboratory (LungAnalysis, Erasmus MC, The Netherlands). Before sending the chest CT scan, in DICOM format, to the central reading facility, the CT scan must be deidentified and coded by the study site. For those sites not familiar with deidentification instructions of chest CT scans, the central reading facility can consult and assist in the deidentification process.

For transfer of the deidentified chest CT scan, the central reading facility will use a Safe File Transfer Protocol. For secure large dataset transfer, SFTP file transfer will be used on web browser SURFfilesender services using data transfer vouchers. The options for secure transfer of the chest CT images will be described in the CT Scan Manual.

After transfer, LungAnalysis will perform a quality assessment of the CT scan(s). Next, the chest CT scan will be evaluated by a certified observer to confirm the diagnosis of bronchiectasis using the BE-CT scoring system. In case no or only minor bronchiectasis is identified using the BE-CT scoring system, the CT scan will be evaluated by a board-certified LungAnalysis chest radiologist on the presence or absence of bronchiectasis.

The screening for bronchiectasis will be determined using the BE-CT method. Each lobe will be assessed for presence and extent of bronchiectasis, as follows:

- 0=no bronchiectasis
- 1=bronchiectasis present in 0% to 32% of the lung lobe
- 2=bronchiectasis present in 33% to 66% of the lung lobe
- 3=bronchiectasis present in 67% to 100% of the lung lobe

The lingula will be assessed as the sixth lung lobe. Hence, the maximum BE-CT score is $6 \times 3 = 18$. In case of a BE-CT score of 3 or lower, a reassessment by a chest radiologist will be performed.

7.6.1. CT Scan Substudy CT Scan Assessment

A subgroup of adult subjects will be included in an evaluation of lung damage through high-resolution CT scan at enrollment (Screening Visit) and EOT (Week 52). Those subjects will have a guided inspiratory and expiratory CT scan done during the Screening Period and at the end of 12 months of treatment. Approximately 225 subjects (75 subjects per study arm) will be included in the substudy. A CT Scan Substudy Manual will be provided to the sites.

All sites participating in the CT substudy will be certified through the LungAnalysis Core Laboratory. The certification includes the following:

1. Certification of the site personnel involved in the CT scan substudy:
    a. Respiratory Therapy Personnel: Training and coaching of the study subjects for the breathing maneuvers during the chest CT acquisition.
    b. Site Radiologist: Compliance with the CT requirements and quality control of the imaging data.

c. Site Pulmonologist: Compliance with the study protocol, including the training and coaching of study subjects.

2. Characterization of the CT scanner that will be used for the study (at the Screening Period and end of treatment [Week 52]) at each site, and definition of the specific chest CT protocol for that scanner:

   a. Specific procedures will be developed for each site, as determined by the scanner model, specification, and study requirements.
   b. A phantom scan will be made using the specified chest CT protocol for calibration purposes.

7.6.2. Image Analysis in the CT Scan Substudy

7.6.2.1. BEST-CT Scoring Method

The BEST-CT scoring method was developed specifically for NCFBE to phenotype the chest CT and to assess the severity of structural lung changes. The training and assessment of observers for BEST-CT is well standardized. CT scans are analyzed in batches and in random order by 2 trained and certified observers. BEST-CT is a grid-based scoring system (software program: Saldsegvol). For inspiratory scans a grid is placed on a minimum of 10 equally spaced axial CT slices (size dependent), and the content in each grid box is annotated according to the following subscores in a hierarchical order:

1. Atelectasis or consolidation
2. Bronchiectasis with partial mucus plugging
3. Bronchiectasis without mucus plugging
4. Airway wall thickening
5. Mucus plugging
6. Ground-glass opacities
7. Emphysema or bullae
8. Healthy airways
9. Healthy parenchyma

Each subscore is expressed as a percent of the total lung volume. For the diagnosis of bronchiectasis, the sum of bronchiectasis with and without mucus plugging should be higher than 0.

The observers are trained for this scoring method by completing a training module consisting of standardized scoring instructions and by analyzing 20 training CT scans in 4 batches. The performance of the observer is evaluated after completing a batch of 5 CT scans and the observer receives feedback from gold standard scores for corrections.

7.6.2.2. Airway-Artery Method

7.6.2.2.1. Manual Airway-Artery Method

For each CT scan, all visible airways are segmented semi-automatically. Next, the bronchial tree is reconstructed in a 3D-view, and cross sectional CT reconstructions are generated based on the airway's center-line. One measurement per airway branch is made when both airways and artery are clearly visible. AA pairs with movement artifacts or too much noise for reliable measurements are excluded. In addition, AA pairs of airways that do not show a visible inner lumen (eg, due to mucus plugging) and airways without a clear identifiable adjacent artery (eg, due to atelectasis or severe cystic bronchiectasis without a traceable artery) are excluded. Inner and outer airway diameters are divided by artery diameter to compute ratios. Wall thickness (difference between outer and inner airway diameter) is divided by the artery diameter to compute its ratio. The manual method is time consuming (8 to 16 hours analysis time per CT scan). The number of AA pairs that can be assessed ranges between 500 and 1000 AA pairs.

7.6.2.2.2. Automated Airway-Artery Method

The process as described for the manual method is done automatically. The system automatically segments all visible airways and arteries and identifies AA pairs. Next, the system automatically measures AA dimensions at multiple positions for each airway segment.

CTs for the brensocatib study will be analyzed automatically. For quality assurance, 5 scans will be measured manually and compared to the automated method.

8. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic samples will be collected from all adult subjects enrolled in the study (Section 8.2), and sputum PD samples will be collected from all newly enrolled adult subjects (Section 8.4.1).

A PK/PD substudy will be conducted at a select number of sites in subjects who are not receiving cyclic antibiotics at Baseline. Subjects who agree will undergo intensive PK and PD sampling (Section 8.2 and Section 8.4). Approximately 300 adult subjects and all adolescent subjects will be included in the PK/PD substudy).

8.1. Pharmacokinetic Endpoints

Non-compartmental PK parameters will not be determined in this study. Population PK analysis will be conducted using a nonlinear mixed-effect model. PK parameters, such as C_{max}, AUC, elimination $t_{1/2}$, CL/F and Vz/F, etc., as appropriate, will be estimated via simulated concentration data. The scope of the analysis will be described in a PK/PD analysis plan.

8.2. Pharmacokinetic Sampling

Predose blood PK samples will be collected from all subjects on Day 1, Week 4, Week 16, Week 28, Week 40, and Week 52, with an optional 2-hour (±30 minutes) postdose sample collected at select visits (ie, Day 1, Week 4, Week 28, and Week 40). NOTE: While collection of the 2-hour postdose PK sample is optional, it is valuable for PK evaluation; therefore, collection of the 2-hour postdose sample is highly recommended.

A PK substudy will be conducted at a select number of sites in subjects who are not receiving cyclic antibiotics at Baseline. Pharmacokinetic samples will be collected at 0 (predose), 0.5 hour (±10 min), 2 hours (±30 min), and 4 to 8 hours postdose on Day 1 and Week 28. At Week 4 and Week 40, PK samples will be collected at predose and 2 hours (±30 min) postdose. At Week 16 and Week 52 visits, PK will be collected at predose only. Before blood PK sampling is conducted, the site staff will review the dosing diary and record the dosing time for the last 2 days.

The details of the blood PK sampling scheme are described in Appendix 5.

All subjects will be advised to do their best to take their study drug around the same time every day. On the day of PK sample collection, the date and time of the previous 2 doses should be recorded.

Blood PK samples will be collected into vacutainers with K_2EDTA. Detailed instructions for PK sample collection, processing, labeling, storage, and shipping will be provided in the Study Laboratory Manual.

Pharmacokinetic samples will be stored frozen (-20°C or lower) until shipment. Plasma concentration of INS1007 will be analyzed using a validated LC-MS/MS method.

8.3. Pharmacodynamic Endpoints

Sputum: The concentration change from Baseline for active NE, CatG, and PR3 in sputum will be evaluated.

Blood: In a small subset of subjects, changes from Baseline for active NE, CatG, and PR3, and other neutrophil functions in blood will be evaluated.

8.4. Pharmacodynamic Sampling

Detailed instructions for PD sputum and blood sample collection, processing, labeling, and storage are provided in the Study Laboratory Manual. Details of the PD sampling scheme for sputum and blood are described in Appendix 6.

8.4.1. Sample Collection for Biomarkers in Sputum

Sputum samples for analysis of NE, CatG, and PR3 will be collected at the following time points:

- Screening Visit
- 0 hour (predose) on Day 1, Week 4, Week 16, Week 28, Week 40, and Week 52
- Week 56 (Follow-up Visit)

8.4.2. Sample Collection for Biomarkers in Blood

Blood samples for analysis of NE, CatG, PR3 and other neutrophil functions will be collected at the following time points:

- Screening Visit
- 0 hour (predose) on Day 1, Week 4, Week 16, Week 28, Week 40, and Week 52
- At Week 56 (Follow-up Visit)

8.5. Pharmacokinetic-Pharmacodynamic Endpoints

Pharmacokinetic-efficacy relationships (eg, PEs and concentrations of active NE in sputum) will be explored using a population PK-PD approach.

Pharmacokinetic-safety relationship (eg, AESI) will be explored using a population PK-PD approach.

The analysis plan will be described in a PK/PD SAP.

9. ASSESSMENT OF SAFETY

9.1. Vital Signs and Pulse Oximetry

Five-minute sitting BP (systolic and diastolic blood pressures), pulse rate (bpm), body temperature (°C), respiration rate (breaths per minute), and oxygen saturation will be recorded in the eCRF at the Screening Visit, and at all in-clinic study visits, as specified in the Schedule of Assessments (Table 5).

9.2. Physical Examination, Height, and Weight

A physical examination of the head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system, and, as appropriate, other body systems will be performed during the Screening Visit (Visit 1) and at Week 52 (Table 5). Any abnormalities noticed at Screening will be recorded in the medical history or as AE if occurred after randomization. The physical examination will also include measurement of height, body weight, and calculation of BMI. Body weight will be measured at the Screening Visit (Visit 1) and at the Week 52 Visit (Visit 11; EOT). For adult subjects, the measurement of height, without shoes, will be performed at the Screening Visit only. For adolescent subjects, measurement of height, without shoes, will be performed at the Screening Visit and Visit 11 (EOT).

9.3. Chest CT Scan

A high-resolution chest CT scan will be performed at the Screening Visit if the subject does not have prior radiological confirmation of NCFBE diagnosis or if the available CT scan was obtained more than 5 years prior to the subject's Screening Visit or the existing CT scan cannot be read due to quality issues (Table 5). A prior chest CT scan may be used if this CT scan was obtained within 5 years from the subject's Screening Visit.

9.4. Electrocardiogram

A 12-lead ECG will be performed at Screening, Baseline, Weeks 4, 28, 40, and 52 (EOT) (Table 5). It is recommended to obtain the 12-lead ECG before PFT by spirometry when scheduled at the same visit.

9.5. Clinical Laboratory Assessments

Clinical laboratory tests of hematology, blood chemistry, and urinalysis will be performed via the study-designated laboratory at the Screening Visit, Baseline, and at all in-clinic study visits, as specified in the Schedule of Assessments (Table 5). The clinical laboratory test parameters are listed in Table 6.

Table 6: Clinical Laboratory Parameters

Category	Laboratory Parameters
Clinical Chemistry	Sodium, chloride, potassium, CO_2, magnesium, calcium, glucose, phosphate, total bilirubin (with direct and indirect fractionation, if total bilirubin is elevated > 2 × ULN), alkaline phosphatase, LDH, AST, ALT, albumin, total protein, creatinine, urea-nitrogen, uric acid, estimated glomerular filtration rate from the Chronic Kidney Disease - Epidemiology Collaboration equation formula (described in Section 9.9)
Hematology	Hemoglobin, erythrocytes, hematocrit, MCH, MCV, MCHC, leukocytes, differential blood count of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets
Urinalysis	Qualitative analysis of glucose, ketones, nitrites, protein, pH, leukocytes, blood, bilirubin, specific gravity; microscopic examination for cells, casts, and bacteria
Special Tests	For WOCBP ≤45 years, a testing of FSH level is required at Screening; a threshold of >40 mIU/mL should be met to be considered infertile

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CO_2=carbon dioxide, FSH=follicle-stimulating hormone, LDH=lactate dehydrogenase, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, ULN=upper limit of normal, WOCBP=women of childbearing potential.

9.6. Dental Hygiene Education

Dental hygiene education includes instruction in daily brushing and flossing. Subjects will be reminded at every visit on the need to maintain an appropriate dental hygiene.

If there are any signs or symptoms of gingivitis or periodontitis that warrant further evaluation upon Investigator discretion, the subject will be referred to a dentist/periodontist for further assessment. The oral and dental evaluation by the dentist for the subject should be assessed thereafter on an interval per the dentist's discretion until EOS Visit.

9.7. Serology Tests

Testing for HBcAb, HBsAb, HBsAg, HIV, and HCV will be conducted at Screening only.

9.8. Serum or Urine Pregnancy Test

A serum pregnancy test will be performed on WOCBP at Screening. A urine pregnancy test will be performed on WOCBP on Day1 (Baseline) and all other visit days, as specified in the Schedule of Assessments (Table 5). In addition to the pregnancy tests required by the Schedule of Assessments, monthly urine pregnancy tests should be conducted by WOCBP in countries where it is required by a local health authority. Adolescent female subjects who reach menarche during the course of the study should undergo urine pregnancy testing at the next clinic visit and at all following clinical visits (monthly where required by local health authority).

Please note that for days of Phone Visits (and monthly home tests, where applicable), WOCBP will be provided with urine pregnancy kits; the test should be performed at home on the day of the Phone Visit (or on the scheduled monthly frequency, where applicable) and the results reported to the site.

Women not of childbearing potential are defined as pre-menarche, postmenopausal (ie, amenorrheic for at least 1 year), or surgically or naturally sterile.

9.9. Estimated Glomerular Filtration Rate

The eGFR calculation per CKD-EPI equation will be analyzed for each subject at Visit 1 (Screening) and at Week 16, Week 28, and Week 52 (EOT).

The CKD-EPI equation described below will be used to calculate the eGFR of creatinine clearance in mL/min.

GFR = 141 × min (Scr/κ, 1) α × max (Scr/κ, 1)-1.209 × 0.993 Age × 1.018 [if female] × 1.159 [if Black]

where:

Scr is the serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr/κ or 1,
max indicates the maximum of Scr/κ or 1.

9.10. Adverse Events

The Investigator is responsible for detecting, documenting, and reporting AEs (refer to Section 9.10.1 and Section 9.10.2 for the definition of AEs and SAEs, respectively).

The Investigator remains responsible for following up all AEs. At the EOS Visit, the Investigator will record the AE status (stable or unstable) in the eCRF.

9.10.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to 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 a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994). Protocol-defined PEs (Section 7.1) are collected as efficacy endpoints via the eCRF. These events should not be reported as AEs unless they fulfill a seriousness criterion.

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings that should be considered AEs.

9.10.2. Definition of a Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatment requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.10.3. Adverse Event of Special Interest

AESIs are defined as events known as related to treatment with DPP1 inhibitors. Additional information on AESIs will be collected in the eCRF. The AESI category groups and preferred terms include the following: hyperkeratosis, infection, and periodontal/gingival events.

9.10.3.1. Hyperkeratosis

The subjects' skin will be monitored throughout the study.

At each study visit the Investigator (or designated healthcare professional in case of a public health emergency) will perform a careful skin evaluation, especially of the palmar and plantar surfaces, the dorsal surfaces of the hands and feet, the Achilles tendon area, knees, and elbows. If there are any signs or symptoms of hyperkeratosis or erythema or deterioration of the pre-existing conditions that warrant further evaluation upon Investigator discretion, the subject will be referred to a dermatologist for further assessment. The skin evaluation by the dermatologist for the subject should then be assessed thereafter on an interval per the dermatologist discretion until the end of the study.

Skin exfoliation or signs of skin thickening in the palms, soles, dorsum of the hands and feet, Achilles tendon area, knees, or elbows should always warrant evaluation by the dermatologist.

Decisions to discontinue the subject from the study will be made by the Investigator after consulting with the dermatologist. Upon receiving the dermatologist's evaluation, the

Investigator should decide whether to continue the subject in the study or initiate early discontinuation of the subject.

9.10.3.2. Periodontitis/Gingivitis

Adult subjects will be advised to conduct self-monitoring of their oral soft tissue, gingiva, and tooth mobility, and report any findings. For adolescents, oral and dental inspection for any signs or symptoms of gingivitis or periodontitis will be performed by the Investigator at each visit.

Occurrence of periodontitis during the study will be considered an AESI. If there are any signs or symptoms of periodontitis or gingivitis that warrant further evaluation upon Investigator discretion, the subject will be referred to a dentist/periodontist for further assessment and treatment. Subjects will be discontinued from the trial if they develop severe periodontal disease as defined by:

- Pocket depth measurement and attachment loss ≥6 mm on 2 or more teeth
- Have Class 3 mobility or Class 3 furcation involvement

9.10.3.3. Other Infections

Subjects will be monitored throughout the study for potential infections. Any severe infection, defined as any infection requiring treatment with parenteral antibiotics/antiviral/antifungal agent, any clinical endoparasitosis, and any opportunistic infection should be considered as AESI. Generally, all uncommon, atypical, or unusually persistent infections should be reported as AESIs.

Note: Pulmonary exacerbations do not fall into this AESI category. Protocol-defined PEs are collected as efficacy endpoints (Section 9.10.1).

Pneumonia will be a specific subcategory within the other infections AESI and will be monitored through the study.

9.10.4. Assessment of Severity

The following definitions should be used to assess intensity of AEs:

- Mild: Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject's usual function.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject's usual function.

9.10.5. Assessment of Causality

The Investigator who identifies an AE will determine the causality of each based on the temporal relationship to administration of study drug and clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related**: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug;

that disappears or decreases on cessation or reduction in study drug dose; and/or that reappears or worsens when the study drug is administered. Could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

- **Not Related**: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

9.10.6. Assessment of Adverse Event Outcome

The Investigator will record the outcome of the AE as either resolved or ongoing on the AE page of the eCRF. Adverse events of unknown outcome or resolution date will be followed until resolved, condition has stabilized, or is no longer clinically relevant.

9.11. Reporting Requirements

9.11.1. Adverse Events

All AEs will be reported on the Adverse Events Form of the eCRF. Adverse events that occur between the time subject signs the ICF for the study and the time when subject receives his/her first dose of study treatment on Day 1 will be summarized as medical history and not as a TEAE unless the event meets the definition of an SAE as defined below.

9.11.2. Serious Adverse Events

All SAEs, regardless of causality, must be reported to the organization delegated by the Sponsor on a Serious Adverse Event Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 24 hours as well.

Study-specific email address and back-up fax number for SAE reporting information:

- Email: safety@insmed.com
- Back-up fax number: 1-908-450-1549

Unexpected drug related SAEs as assessed by Sponsor or authorized person qualify for expedited reporting and will be reported to the IRB/EC, regulatory authorities, participating Investigators and, if cross reporting is required for SUSARs, in accordance with all applicable global laws and regulations. A SUSAR is a Serious Adverse Reaction, which is suspected to be caused by the investigational medicinal product and which is unexpected, ie, its nature or severity is not consistent with the information in the relevant Reference Safety Information. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the regulatory agencies as appropriate (ie, for the FDA these are reported in the Investigational New Drug annual report and for the European Medicines Agency, these are reported in the Development Safety Update Report).

9.11.3. Pregnancy

Any pregnancy, including the pregnancy of a male subject's female partner, that occurs during any phase of the study must be reported to the Sponsor or designated organization within 24 hours of learning of the pregnancy using a Clinical Study Pregnancy Form.

The study treatment should be discontinued for female subjects only, and the pregnancy should be followed to term. The details of termination must also be reported, including details of birth, the presence or absence of birth defects, congenital abnormalities or maternal and newborn complications, or whether termination was spontaneous or voluntary.

9.11.4. Overdose

An overdose is defined as a dose greater than the dose level(s) evaluated in this study. An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires an expedited reporting as if it is an SAE. In the case of a symptomatic overdose, the Investigator should use clinical judgment in treating the overdose and should inform the Sponsor immediately. The Investigators should refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study treatment used in the study. Such documents may include, but not limited to, the Investigator's Brochure.

9.12. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to follow-up on each subject who experienced the AE at subsequent visits or contacts.

Unless the subject is lost to follow-up (as defined in Section 4.2.2.3), all subjects with SAEs will be followed until the SAE is resolved, stabilized, or the event is otherwise explained.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

9.13. Regulatory Aspects

The Sponsor has a legal responsibility to notify the United States Food and Drug Administration, National Competent Authorities, and Central Ethics Committees of the European Union, and any other foreign regulatory competent agency, as well as all sites, about the safety of the drug. The Investigator has the responsibility to notify the local IRB/IEC about SUSARs.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents. Copies of the notification to the ethics committee must be sent to the Sponsor.

10. STATISTICS

A detailed SAP will be developed for this study. The SAP will be finalized and approved prior to the database lock.

This study will include approximately 1620 adult subjects with NCFBE. In addition, approximately 40 adolescents will be randomized to provide an adequate description of the safety profile of brensocatib in this age group and offer the possibility to observe directional trend in terms of efficacy. In the interest of providing information to prescribers on the use of brensocatib in adult patients in a timely fashion, the planned database lock is based on the time when the targeted 1620 adult subjects (originally planned sample size) complete the 52-week treatment period or discontinue from the study before Week 52, irrespective of whether the adolescent subjects have completed the study. All adult and adolescent data collected up to this database lock will be included in the primary efficacy and safety analyses for the CSR. Additional data collected between database lock and the last adolescent subject completing the last visit will be summarized in a CSR addendum. Any additional analyses of efficacy and safety data will be detailed in the SAP.

All of the efficacy and safety data that have already been collected from 44 Ukraine subjects impacted by the war in Ukraine will be listed only and not included in the formal efficacy and safety analyses, as agreed with FDA and EMA.

10.1. Sample Size and Power Considerations

The study is designed to demonstrate superiority of brensocatib treatment at 10 mg and/or 25 mg over matching placebo as measured by the primary efficacy endpoint of the rate of PEs over the 52-week treatment period. Assuming the annualized PE rate in the placebo arm is 1.2 events with a negative binomial distribution with dispersion of 1, 1620 adult subjects will yield 90% power if the ratio of exacerbation rate is 0.70 (brensocatib over placebo) between any of the brensocatib treatment arms and placebo after 52 weeks of treatment. This estimate is based on study-wise two-sided Type I error of 0.01 or 0.005 for each primary comparison between brensocatib and placebo.

Randomization will be stratified based on a geographic region (North America, Europe, Japan, and the Rest of the World), Screening sputum sample positive or negative for *Pseudomonas aeruginosa*, and the number of prior PEs (2, or ≥3) in the previous 12 months.

It is well known that among subjects with NCFBE, there is significant heterogeneity across regions in terms of distribution of phenotypes, baseline lung function, symptom scores, presence of comorbidities, and treatment patterns (Jauhiainen et al., 2020; Rabe et al., 2019).The ASPEN study was launched with a global outreach to more than 30 countries so that meaningful conclusions could be drawn on the effect of brensocatib in a representative population. Furthermore, the study was designed to ensure an adequate representation of all types of standards of care and of individual phenotypes worldwide.

In order to have a representative population of NCFBE across all regions, enrollment targets have been established for adult subjects. Up to 13% of subjects will come from Eastern Europe. North America, Western Europe, Asia Pacific, and Latin America will contribute between 20%

and 30% each. No single country (except the US) will contribute more than 15% of the overall randomized population.

In order to have a representative population in the study, similar to what is described in the literature, randomization will be enforced to have approximately 30% of adult subjects with 3 or more prior PEs, to have no more than 20% of subjects older than 75 years of age, to have approximately no more than 20% of subjects with eosinophil count in peripheral blood $\geq 300/mm^3$ at Screening, and to have no more than 20% of subjects with COPD as a comorbidity.

The adolescent sample size of approximately 40 subjects is based on the Sponsor's consultation with several pediatric investigators in this field and from a survey across a number of global sites with pediatric experience conducted by the study CRO; the sample size also takes into consideration the potential challenges with enrollment and the low prevalence of the disease in this age group. The sample size is expected to provide a description of the safety profile of brensocatib in this age group and offer the possibility to observe directional trends in efficacy.

The PK/PD substudy will include approximately 300 adult and 40 adolescent subjects who are not receiving cyclic antibiotics at Baseline; the sample size is based on clinical considerations.

The CT substudy will include approximately 225 adult subjects; the sample size is based on clinical considerations.

10.2. Analysis Sets

10.2.1. Screened Analysis Set

The Screened Analysis Set comprises all subjects who provide written informed consent.

10.2.2. Intent-to-Treat Analysis Set

The ITT Analysis Set comprises all subjects who were randomized subjects. This set will be analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received.

10.2.3. Safety Analysis Set

The Safety Analysis Set comprises all participants who were randomized and received at least 1 dose of brensocatib or placebo. The Safety Analysis Set will be analyzed using the actual treatment received.

10.2.4. Pharmacodynamic Analysis Set

The PD Analysis Set comprises subjects who have consented to participate in the PD substudy, have received at least 1 dose of study drug, and have at least 1 predose and 1 postdose measurement of biomarkers. The PD Analysis Set will be analyzed using the actual treatment received.

10.2.5. Pharmacokinetic Concentration Analysis Set

All subjects with PK postdose data, either in the main study or PK/PD substudy, will be included in the PK Concentration Analysis Set. The PK Concentration Analysis Set comprises participants who have consented to participate in the PK substudy, have received at least 1 dose of

brensocatib, and have at least 1 postdose plasma concentration of brensocatib. Participants will be classified according to treatment received regardless of the treatment group to which they were randomized.

10.2.6. CT Scan Analysis Set

The CT Analysis Set comprises subjects who have both Baseline and postbaseline CT measurement data.

10.3. General Considerations

All original and derived parameters as well as demographic and disposition data will be listed and tabulated using descriptive statistics. Frequency counts (n and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, SD, median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All data will be summarized by treatment where appropriate. In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data.

Data will be pooled across centers and countries within a region.

Baseline is defined as the last observation before or on the randomization date, unless otherwise specified.

Statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, NC, US) Version 9.4 or higher unless otherwise specified.

10.4. Statistical Analysis

10.4.1. Subject Disposition

Subject disposition will be listed and summarized including the number and percentage of subjects completing or prematurely discontinuing the treatment and/or study and the primary reason for withdrawal. Subjects excluded from any analysis sets will be listed including the reasons for exclusions.

Demographic data and baseline characteristics will be summarized and presented in data listings.

10.4.2. Medical History

Medical history will be presented in data listings.

10.4.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded by Preferred Term using the World Health Organization Drug Dictionary (WHODRUG). Prior medications are defined as those taken before the first dose of randomized drug. Concomitant medications are defined as any medication, taken after the first dose of randomized drug, or those starting before but continuing after. Prior and concomitant medications will be summarized and presented in data listings.

10.4.4. Major Protocol Deviations

The major protocol deviations will be identified based on a review of the study data prior to the database lock and unblinding. Major deviations may include the following:

- Violation of inclusion and/or exclusion criteria;
- Noncompliance with the dosing schedule (ie, subjects for whom compliance during the double-blind treatment period was not between 75% and 120%);
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoints.

Major protocol deviations will be summarized and presented in data listings.

10.4.5. Treatment Exposure and Compliance

The cumulative exposure to study drug, including duration of treatment, total number of doses received, and cumulative amount of drug received (mg), will be summarized by treatment group.

Treatment compliance will be calculated as:

Compliance (%) at Visit X = (Number of doses taken up to the day preceding Visit X /

Number of expected doses up to the day preceding Visit X) * 100
Treatment compliance will be listed by subject and summarized by treatment, based on the Safety Analysis Set.

10.4.6. Efficacy Analyses

10.4.6.1. Analysis of Primary Efficacy Endpoint

10.4.6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the annualized rate of PEs that have been confirmed through the event adjudication process.

A minimum of 14 days must occur between the end date of one pulmonary exacerbation and the start date of the next pulmonary exacerbation. Any exacerbations that occur less than 14 days from the prior exacerbation will not be considered a new exacerbation. Any adjudicated PE that meets the protocol criteria after randomization through the end of study will be included in the primary endpoint calculation.

Subject's time at risk will be the time on study excluding the time during exacerbations.

10.4.6.1.2. Main Analysis for Primary Endpoint

The primary estimand is the On-Study estimand in which all observed data up to Week 52 will be included in the analysis. The ITT Analysis Set will be used for this estimand.

The rate of PEs will be analyzed using negative binomial regression with robust estimate for the covariance matrix. The model will include treatment group and the randomization stratification factors (geographic region [North America, Europe, Japan, and the Rest of the World], sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PEs [<3 or ≥3] in the previous 12 months), and age group (adult, adolescent) as fixed effects. If the age group covariate creates estimability issues, it may be removed. The time at risk (log scale) will be included in the model as an offset variable.

The annualized rate of PE (PEs per subject per year; #PEs/time at risk * 365.25) for each treatment group, the ratios of PE rates between each brensocatib dose and placebo, and the associated 95% CIs will be estimated from the negative binomial model.

10.4.6.1.3. Sensitivity Analyses for Primary Endpoint

Sensitivity analyses will be conducted to assess the robustness of the primary results in the presence of missing data.

In the event that there are study participants who discontinue randomized IP early and also decline to remain in the study, ascertainment of data will be incomplete, and a true treatment policy/ITT analysis cannot be achieved. A MAR assumption for the missing data is made implicitly for the On-Study estimand using the observed data alone, and a hypothetical strategy is inherently implemented for the ICEs of early study withdrawn.

The main analysis using the negative binomial model is unbiased under the MAR assumption for the missing data. However, in some instances, the fact that data are missing may be directly related to the unobserved values (ie, MNAR). Therefore, robustness of the main analysis to departures from the MAR assumption will be assessed using tipping-point analyses. Due to the inherent difficulties in identifying the missing data mechanism in practice, all missing data will be assumed MNAR, and the tipping-point penalties will be applied accordingly.

Full details of the sensitivity analyses will be described in the SAP.

10.4.6.1.4. Supportive Analyses for Primary Endpoint

The supportive estimand for the primary endpoint is the On-Treatment estimand and will utilize the ITT Analysis Set. The same negative binomial regression model will be implemented for this estimand; however, only data up until the occurrence of a relevant ICE (ie, early discontinuation of randomized study treatment, early discontinuation of standard of care, or addition of chronic antibiotics) will be included in the analysis. Time at risk will be defined as the time of exposure until the occurrence of an ICE or until the last dosing date of IP if no ICE occurred. Time during an exacerbation will be excluded from the time at risk.

10.4.6.2. Analysis of Secondary Efficacy Endpoints

10.4.6.2.1. Main Analysis of Secondary Efficacy Endpoints

All inferential analyses for PE-related endpoints will be based on PEs that have been confirmed through the adjudication process. The primary estimand for the secondary endpoints will be On-Study estimand in which all observed data (ITT Analysis Set) will be included in the analysis.

- For time to first PE, the survival curves will be compared between the brensocatib dose and placebo using a Cox proportional hazards model based on the ITT Analysis Set. The covariate will include the stratification factors used for the randomization (see Section 10.4.6.1).
- For the proportion of subjects who are exacerbation free, the comparison between brensocatib and placebo will be analyzed using logistic regression with treatment group and randomization stratification factors as fixed effects.

- Absolute change from Baseline in postbronchodilator FEV_1 will be analyzed using linear repeated measures model with fixed effects of treatment, stratification factors as noted above, visit, treatment-by-visit interaction, as well as the continuous, fixed covariate of Baseline value. An unstructured variance-covariance matrix will be fit.
- Rate of severe PEs will be analyzed using the same method as the primary endpoint.
- Change from Baseline in the QOL-B Respiratory Symptoms Domain scores will be analyzed using linear repeated measures model with fixed effects of treatment, stratification factors, visit, treatment-by-visit interaction, as well as the continuous, fixed covariate of Baseline value. The variance-covariance structure will be compound symmetric with the robust sandwich variance estimator. The subgroup of adult subjects will be included in the analysis because the QOL-B is completed by adult subjects only.

Further analysis details and sensitivity analyses as well as supplementary analyses for secondary endpoints will be described in the SAP.

10.4.6.3. Analysis of Exploratory Endpoints

Other exploratory endpoints will be analyzed using the methods suitable for the type of endpoint. Further details will be described in the SAP.

10.4.6.4. Adjustment of Multiplicity for Efficacy Analysis

In this study, the enhanced mixture-based gatekeeping procedure (Kordzakhia et al, 2018) will be used as the multiplicity adjustment method to control the overall type I error rate at a full alpha ($\alpha = 0.05$) with a two-sided test for the multiple tests of the primary and secondary endpoints across the two brensocatib doses relative to placebo. The enhanced mixture-based method is based on the closed testing procedure and thus protects the overall type I error rate in a strong sense. Adjusted p-values will be reported.

To demonstrate substantial evidence of effectiveness, the adjusted p-values for the comparisons of brensocatib 25 mg versus placebo and brensocatib 10 mg versus placebo for the primary endpoint, the annualized rate of PEs, will also be compared against the two-sided $\alpha = 0.01$.

Rejecting either or both null hypotheses and accepting the corresponding alternative hypotheses with lower rate of PEs in the brensocatib treatment arms, for the ITT Analysis Set, will be considered as a successful demonstration of efficacy. Full details of the multiplicity adjustment process of the enhanced mixture-based gatekeeping procedure will be described in the SAP.

10.4.6.5. Subgroup Analyses

Consistency of observed treatment effect on the rate of PEs will be explored across major subgroups as shown in the list below, if deemed appropriate.

- Age (12 to <18 years, 18 to <65 years, ≥65 years; <75 years, ≥75 years)
- Sex (Male, Female)
- Race (White, Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, Other)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Number of PEs in prior 12 months (1, 2, or ≥3)
- Chronic use of antibiotics at Baseline (Yes, No)
- Maintenance use of macrolides at Baseline (Yes, No)
- *Pseudomonas aeruginosa* colonization status at Baseline (Positive, Negative)
- Baseline BSI score (≤4, 5 to 8, ≥9)
- Baseline BSI score (< median, ≥ median)
- Baseline CT scan score (< median, ≥ median)
- Baseline FEV_1 % Predicted (<50%, ≥50%)
- Geographical region (North America, Europe, Japan, the Rest of World).

Subgroup analysis will be based on a negative binomial model as used for the primary analysis. One model per subgroup will be fitted, omitting the fixed effect if it is identical to the subgroup. The ITT Analysis Set will be used. A summary for each level of subgroup presenting the same data as for the primary analysis will be produced. A forest plot of subgroups with rate of PEs and 95% CI displayed for each level of subgroup.

The main analysis for the primary and secondary endpoints will be repeated for the adolescent subgroup (12- <18 years of age), and separately for the adult subgroup for the On-Study estimand.

Additional subgroup analyses may also be performed if deemed appropriate.

10.4.7. Safety Analysis

All safety data will be summarized by treatment received using descriptive statistics based on the Safety Analysis Set. All safety data will be listed for each subject as well.

10.4.7.1. Adverse Events

Adverse events will be coded using MedDRA. Treatment-emergent adverse events will be summarized by SOC and PT by treatment group. Non-emergent adverse events will be presented in the data listings.

The number and percentage of subjects with AEs will be presented by treatment and dose group.

The severity of AEs, the relationship to study drug, AEs causing study discontinuation, and SAEs will be similarly presented. All AEs reported during the study will be listed.

10.4.7.2. Clinical Laboratory Tests

All clinical safety laboratory data (blood chemistry, hematology, and urinalysis) will be listed for each subject. Laboratory values outside the normal ranges will be flagged. If applicable, summary statistics (mean, range) for actual values and change from Baseline by treatment will be provided for each time point.

10.4.7.3. Vital Signs

Vital signs will be listed and summarized including actual values and changes from Baseline.

10.4.7.4. ECGs

Heart rate and corrected QT interval by Fridericia's formula will be derived from the dECG at each time point. The dECG data will be listed and summarized descriptively; outlier analyses for QTcF will also be performed.

10.4.8. Pharmacodynamic Analysis

The NE activity in sputum and blood will be calculated as percentage inhibition from the pretreatment activity. The pretreatment value is defined as the mean value of NE activities at Screening and Baseline and will be listed and summarized. All other biomarker levels at pre- and postdose levels will be listed and summarized.

Pharmacodynamic parameters that are planned to be analyzed are NE, CatG, PR3, and neutrophil functions including oxidative and bactericidal assays, neutrophil adhesion chemotaxis and others.

The results of NE, CatG, and PR3 activities, neutrophil functions, ANC, and other biomarkers will be listed by subject and time point. Note that ANC will be included in both safety and PD-related analyses.

The observed time to maximum inhibition and maximum inhibition for NE, CatG, and PR3 activities, neutrophil functions and ANC will be reported and listed for each subject. The NE activity in sputum and blood will be calculated as percent inhibition from the pretreatment activity. The pretreatment value is defined as the mean value of NE activities at Screening and Baseline and will be listed and summarized.

Descriptive statistics for NE, CatG, and PR3 activities, neutrophil functions, ANC, and derived activity parameters (maximum inhibition and time to maximum inhibition) will be presented by dose levels of brensocatib and placebo.

Individual figures of NE, CatG, and PR3 activities, neutrophil functions and ANC versus time will be presented with all subjects overlaid on the same plot for each dose level (spaghetti plots). Mean plots versus time will also be presented with all dose levels and pooled placebo overlaid on the same plot.

Plasma concentration data for brensocatib will be pooled with corresponding data from other studies for population PK/PD modeling of the exposure response relationship. The methods and results of any population PK/PD analyses will be described and reported separately.

10.4.9. Pharmacokinetic Analysis

For subjects participating in the PK/PD substudy and subjects with postdose PK samples in the main study, plasma concentrations of brensocatib will be listed and summarized by dose level over each scheduled sampling time using descriptive statistics (including arithmetic mean, SD, median, minimum and maximum, geometric mean, and percent coefficient of variation of the geometric mean, as appropriate). Individual plasma concentration data versus time for the PK/PD substudy will be presented in data listings, along with graphical plots of individual and geometric mean plasma concentration-time plots presented in linear and semi-logarithmic scale.

Actual sampling times and brensocatib plasma concentrations from sparse sampling will be listed but not summarized. The modeling output will be reported outside of the CSR.

Brensocatib plasma concentration data from this study will be pooled with data from other studies for the purposes of developing a population PK model. After an adequate structural model is identified, covariate analysis may be performed to evaluate the effect of intrinsic and extrinsic factors on the PK model parameters.

A detailed SAP for the population PK parameters and reporting will be developed. The PK SAP will be finalized and approved by signature prior to the database lock to preserve the integrity of the statistical analysis and study conclusions.

10.4.10. Population Pharmacokinetic Analysis

Plasma concentration data from this study will be utilized in population PK analysis as an exploratory measure. The individual PK parameters, such as C_{max}, T_{max}, AUC_{0-24}, elimination $t_{½}$, CL/F, and Vd/F, will be determined using a population PK model. PK covariates will be evaluated. The results will be reported separately.

10.4.11. Pharmacodynamic-Pharmacodynamic Analysis

Brensocatib PD data from this study will be pooled with data from other studies for the purposes of developing a population PK/PD model. Covariate analysis may be performed to evaluate the effect of intrinsic and extrinsic factors on the PD model parameters. A stand-alone modeling and simulation analysis plan will be written for the PK/PD and PD models. The modeling output will be reported outside of the CSR.

The relationship between brensocatib PD biomarkers of DPP1 inhibition (eg, NE, CatG, and PR3 levels and neutrophil functions) and outcome measures (ie, PE, FEV_1, etc.) will be explored graphically. If appropriate, linear or nonlinear models may be used to further describe their relationship. In addition to the PD-PD analysis, other analysis methodologies, such as nonlinear mixed-effect modeling, may be employed to further characterize the PD/PD relationship of brensocatib.

10.4.12. CT Analysis

Descriptive statistics will be provided for BEST-CT scores. AA ratio will be presented by brensocatib doses and placebo. The results of BEST-CT scores and AA ratio will be listed by subject and time point.

10.5. Interim Analysis

No interim analysis of efficacy data is planned.

11. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/EC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

11.1. Source Documents

Study data will be collected on source documents. The Investigator is responsible for assuring that collected data are complete and accurate. Source documentation (the point of initial recording of a piece of data) should support data collected on the eCRF. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study.

11.2. Data Collection

All data obtained for this study will be entered into a local regulation (ie, 21 CFR Part 11 in the USA) compliant Data Management System provided by the Sponsor or its designee. These data will be recorded with an EDC system using eCRFs. The Investigator will ensure the accuracy and completeness of the data reported to the Sponsor. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. Data reported in the eCRFs should be consistent with and substantiated by the subject's medical record and original source documents. The eCRF data will be monitored by the Sponsor or designee. The final, completed eCRF Casebook for each subject must be electronically signed and dated by the PI within the EDC system to signify that the Investigator has reviewed the eCRF and certifies it to be complete and accurate.

The Sponsor will retain the final eCRF data and audit trail. A copy of all completed eCRFs will be provided to the Investigator.

11.3. Study Record Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

12. FINANCING AND INSURANCE

12.1. Finances

Prior to starting the study, the Investigator and/or institution will sign a clinical study agreement with Sponsor. This agreement will include the financial information agreed upon by the parties.

12.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

13. STUDY ADMINISTRATIVE INFORMATION

13.1. Financial Disclosure by the Investigator

The disclosed financial interest of the Investigator must be collected before Screening of the first subject, following study completion at the Investigator site and 1 year following overall study completion. The Investigator should promptly update this information if any relevant changes occur during this period.

13.2. Study Registration and Results Disclosure

The Sponsor will provide study information for inclusion in national registries according to national/local regulatory requirements.

Results of this study will be disclosed according to the relevant national regulatory requirements.

13.3. Study Files and Materials

Before the start of any study-related procedures, all initial documents required by ICH GCP, Good Pharmacoepidemiology Practice, and applicable local regulations must be available in the relevant files maintained by the Sponsor (or delegate) and the Investigator. An Investigator Study File prepared by the Sponsor (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigators at each site will be included in the Investigator Study File. The respective files will be kept and updated by the Sponsor (or delegate) and the Investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the Sponsor's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited by qualified delegates from the Sponsor or a competent regulatory authority.

13.4. Use of Stored Samples and Data

Stored samples will be labeled with study and subject information and kept in a locked room with limited access. Electronic data will be kept in password protected computers at the laboratory and then transferred to the Sponsor or CRO, as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's specimen tracking system.

Prior Sponsor and IRB approval are required before using or sharing study samples or data in ways not specifically specified in the study protocol during conduct of this study.

Any loss or unanticipated destruction of samples (eg, freezer malfunction) or data (eg, loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to the Sponsor and the IRB/EC.

At any time, subjects may inform the Investigator that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will

request that all known remaining samples be destroyed and report the disposition of samples to the requesting subjects and the IRB/EC.

At the completion (termination) of the study, samples will continue to be stored for a period of up to 5 years or longer if required by the institution participating in the study. The information already collected, including biological samples, will continue to be used to evaluate the study results and in future medical and pharmaceutical research activities. However, the stored samples will not be used for genetic evaluation unless stated in a separate consent document. Additionally, with subject's consent, samples may be used for further research by Insmed or others such as universities or other companies to contribute to the understanding of NCFBE or other diseases, the development of related or new treatments, or research methods.

13.5. Disposition of Stored Samples and Data

Access to stored samples will be limited by using a locked room. Samples stored by the central laboratories will be labeled with the subject's study identification information. Data will be kept in password protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, if other Investigators may wish to study these samples and/or data, they need to obtain Sponsor approval before any sharing of samples and/or data.

Any loss or unanticipated destruction of samples (eg, due to freezer malfunction) or data (eg, loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to the Sponsor and the IRB/EC.

Additionally, subjects may decide at any point not to have their samples stored for a period of up to 5 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the subject and to the IRB/EC. This decision will not affect the subject's participation in this protocol.

13.6. Initiation of Study

Before the start of the study at each study site, the Sponsor's study monitor (or delegate) shall confirm adequacy of the facilities by study site visit or other acceptable methods.

The Investigator may not enroll any subject into the study before the Sponsor has received written approval or a favorable opinion from the health authority, where applicable, and the EC or IRB for conducting the study and a formal meeting has been conducted by the Sponsor's study monitor (or delegate) to initiate the study. This meeting will include a detailed review of the study plan, and completion of the eCRF.

13.7. Subject Reimbursement, Liability, and Insurance

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

The Sponsor will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, subjects taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

13.8. Subject Identification and Confidentiality

Subject names will not be supplied to the Sponsor. A Subject Number will be recorded in the eCRF, and if the subject name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the Sponsor. All records will be kept confidential to the extent provided by federal, state, and local laws. The subjects will be informed that representatives of the Sponsor, IRB/EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

13.9. Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol, eCRF, IB, and any study-related materials with the Investigators and their staff. During the study, the study Sponsor monitor or its designee will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, adherence to the protocol, adherence to ICH GCP and applicable regulatory requirements, the progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. Subject confidentiality will be maintained by the study center. The study Sponsor monitoring standards require full verification for the presence of informed consent (and assent if required per local requirements), adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

13.10. Protocol Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor, before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies) and IRBs/IECs. Copies of the applicable written approvals must be given to the site monitor or their designee.

The requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the study Sponsor or its agent

should be notified and the applicable regulatory authority(ies)/IRBs/IECs should be informed within 10 working days. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/IRB/EC approval, but the regulatory authority(ies)/IRBs/IECs must be kept informed of such administrative changes in accordance with country-specific requirements.

13.11. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the Sponsor may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform the study Sponsor, immediately that this request has been made.

13.12. Publication Policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of the study Sponsor. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by the study Sponsor and statisticians, and not by the Investigators themselves. Investigators participating in multi center studies agree not to present data gathered from a single center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and study Sponsor.

The study Sponsor must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). The study Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as the study Sponsor personnel.

At the conclusion of the study, after the data are analyzed, the results of study will be reported in a CSR.

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15. APPENDICES

APPENDIX 1. SPUTUM INDUCTION GUIDELINES

Collection of good sputum samples is critical to this study. Sputum samples will be collected at the clinical site. To facilitate the collection of good sputum samples during study visits, sputum induction may be performed at all visits except Screening if the subject is unable to expectorate approximately 3.0 mL of sputum.

Note: If an adult subject is unable to produce sputum spontaneously during Screening (Visit 1), the subject will be considered a screen failure. Adult subjects may not undergo a sputum induction procedure during Screening (Visit 1) to meet eligibility (Section 4.1.1, Exclusion Criterion 6). Adolescent subjects are not required to produce a sputum sample for Screening if they are unable.

Purpose

The purpose of this guideline is to provide recommendations to the clinical sites for obtaining a sputum sample by induction if the subject is unable to expectorate a sputum sample on their own or after chest percussion.

Required Equipment

- Standard handheld nebulizer used in the site or the subject can be asked to bring the nebulizer they use at home for pulmonary hygiene
- The nebulizer should be thoroughly disinfected to ensure no cross-contamination
- Sputum specimen containers with label – sputum collection tube provided by central laboratory
- Sodium chloride solution (saline) – 3% and 7%, and possibly 10%
- Standard clinic supplies (eg, disinfectant/germicidal/alcohol wipes, tissues, paper towels, etc.)

Procedure

General Instructions:

- At the study site, sputum induction should occur in a private, contained room. Specific processes in place at the clinic to prevent contamination and ensure sterilization before and after sputum induction should be followed.
- Clinic personnel should wear gloves and a mask during the entire procedure.
- Only 1 subject should be induced at a time.
- All collection containers should have a sputum collection label clearly completed with subject identifiers, visit name, date and time.
- The subject should have been instructed not to eat at least within 1 hour of sputum induction procedure.
- An explanation should be provided to the subject that the purpose of this procedure is to help him/her cough up a sputum sample and that the success of the procedure is dependent on the subject's active participation.

Inhalation and Collection Procedures:

- The induction procedure should start by utilizing either 3% or 7% saline based on the Investigator's preference.
- Approximately 3 to 6 mL of the selected saline should be placed in the nebulizer.
- The subject should be sitting up or in a semi-Fowler position.
- The subject may wear a nose clip during the nebulization.
- The subject should breathe slowly and deeply through the nebulizer mouthpiece inhaling the salt water mist. Remind the subject not to breathe quickly but to have slow, deep breaths pausing at peak inspiration to allow deposition of particles.
- The nebulization time is 10 minutes.
- At the end of this time, the subject should take a few deep breaths, swallow the extra saliva in his/her mouth and try to cough up a sputum sample.
- The subject should be encouraged to cough forcefully using the deep coughing method and/or "huffing" cough method.
- All sputum should be deposited in the specimen container. The container should not be opened until the specimen is ready to be deposited. The container should be closed immediately after depositing the sample.
- The sputum sample should be approximately 3 mL – slightly below the bottom line (5 mL) on the collection container.
- If a sufficient sputum sample is not collected and the subject appears to be tolerating the induction procedure well, the subject can complete another 10-minute nebulization period.
  - If a second 10-minute nebulization period is required, the recommendation is to increase the sodium chloride concentration (ie, if 3% was used first then 7% should be used for the subsequent nebulization; if 7% was used first then 10% should be used for the subsequent nebulization).
  - Closely monitor the subject for tolerability issues or side effects.
  - No more than two 10-minute nebulization periods should be completed.
- The sputum sample should be refrigerated until it is sent to the microbiology laboratory.

Side Effects

- The subject may experience side effects from the sputum induction procedure. The most common side effects include:
  - coughing
  - sore throat
  - wheezing
  - nausea
  - lightheadedness
  - headache
  - shortness of breath
  - chest tightness
- Other possible side effects include hyperventilation or bronchospasm. For bronchospasm, ensure subject receives the necessary medical management.

Miscellaneous

- If the subject needs to expectorate during nebulization, turn off the nebulizer and allow the subject to cough up sputum into the container. If a sufficient specimen is not collected, the subject should then resume the nebulization to complete the 10minute nebulization duration.
- The subject should be encouraged to blow his/her nose as often as needed during the induction procedure to help prevent nasal sections from becoming mixed with sputum specimen.

APPENDIX 2. CALCULATION OF BRONCHIECTASIS SEVERITY INDEX

Severity Criteria	0 Point	1 Point	2 Point	3 Point	4 Point	5 Point	6 Point
Age (Years)	< 50	-	50 to 69	-	70 to 79	-	80+
BMI (kg/m^2)	> 18.5	-	< 18.5	-	-	-	-
FEV_1 (% Predicted)	> 80%	50 to 80%	30 to 49%	< 30%	-	-	-
Hospital Admissions Due to Bronchiectasis Exacerbation in the Past 2 Years	No	-	-	-	-	Yes	-
Exacerbation Frequency in Last 12 Months	0 to 2	-	3 or More	-	-	-	-
MRC Dyspnea Score[a]	1-3	-	4	5	-	-	-
Colonization Status	Not Colonized	Chronic Colonization	-	*Pa* Colonization	-	-	-
Radiological Severity	< 3 Lobes Involved	3 or More Lobes or Cystic Changes					

Note: Estimated outcomes are those observed across 5 European treatments in the original derivation and validation study (Chalmers et al., 2014).
BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, MRC = Medical Research Council; *Pa = Pseudomonas aeruginosa*.
[a] Use Appendix 3.

APPENDIX 3. THE MEDICAL RESEARCH COUNCIL BREATHLESSNESS SCALE

Grade	Degree of Breathlessness Related to Activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yards or after walking a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

APPENDIX 4. HY'S LAW CASES

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin

INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Insmed clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law (PHL)

AST or ALT ≥3 × ULN and TBL ≥2 × ULN at any point during the study irrespective of an increase in ALP. The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3 × ULN and TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 x ULN
- AST ≥3 x ULN
- TBL ≥ 2 x ULN

The Investigator will review without delay each new laboratory report and if the identification criteria are met will:

- Notify the Insmed representative
- Determine whether the subject meets PHL criteria (see DEFINITIONS of this Appendix) by reviewing laboratory reports from all previous visits

FOLLOW-UP

POTENTIAL HY'S LAW CRITERIA NOT MET

- If the subject does not meet PHL criteria the Investigator will:
- Inform the Insmed representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

POTENTIAL HY'S LAW CRITERIA MET

If the patient does meet PHL criteria the Investigator will:

- Notify the Insmed representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the IMP. The Insmed Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:
- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF

If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the Insmed standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term ‘Hy’s Law’) according to Insmed standard processes.
  - The ‘Medically Important’ serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of ‘related’ should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

REFERENCES

FDA Guidance for Industry (issued July 2009). ‘Drug-induced liver injury: Premarketing clinical evaluation.’

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

APPENDIX 5. SCHEDULE OF PHARMACOKINETIC SAMPLE COLLECTION

Day/Week	Collection Time	Collection Window	All Adult Subjects	Substudy Subjects[a]
Day 1	0 hour (predose)	–	X	X
	0.5 hour postdose	± 10 min	–	X
	2 hours postdose	± 30 min	X (optional)[b]	X
	4 to 8 hours postdose	–	–	X
Week 4	0 hour (predose)	–	X	X
	2 hours postdose	± 30 min	X (optional)[b]	X
Week 16	0 hour (predose)	–	X	X
Week 28	0 hour (predose)	–	X	X
	0.5 hour postdose	± 10 min	–	X
	2 hours postdose	± 30 min	X (optional)[b]	X
	4 to 8 hours postdose	–	–	X
Week 40	0 hour (predose)	–	X	X
	2 hours postdose	± 30 min	X (optional)[b]	X
Week 52	0 hour (predose)	–	X	X

a Additional PK blood samples will be collected from all adult subjects who participate in the PK/PD substudy, and PK blood samples will be collected from all adolescent subjects enrolled in the study. The PK/PD substudy will include subjects who are not receiving cyclic antibiotics at Baseline.

b While collection of the 2-hour postdose PK sample is optional, it is valuable for PK evaluation; therefore, collection of the optional 2-hour postdose sample is highly recommended.

Note: The blood sample collected for all adult subjects will be used for the substudy when substudy sample collection is scheduled at the same timepoint (no extra samples will be collected).

PD = pharmacodynamic; PK = pharmacokinetic.

APPENDIX 6. SCHEDULE OF PHARMACODYNAMIC SAMPLE COLLECTION

Day/Week	Collection Time	All Adult Subjects[a]	Substudy Subjects[b]	
		Sputum Sample	Blood Sample[c]	Sputum Sample[d]
Screening Visit	During Screening Visit	X	X	X
Day 1	0 hour (predose)	X	X	X
Week 4	0 hour (predose)	X	X	X
Week 16	0 hour (predose)	X	X	X
Week 28	0 hour (predose)	X	X	X
Week 40	0 hour (predose)	X	X	X
Week 52	0 hour (predose)	X	X	X
Week 56	At Follow-up visit	X	X	X

a Pharmacodynamic sputum samples will be collected from all newly enrolled adult subjects.
b The PK/PD substudy will include subjects who are not receiving cyclic antibiotics at Baseline.
c PD blood samples will be collected from approximately 40 adult subjects enrolled in the PK/PD substudy at select sites in the United States.
d PD sputum samples will be collected from all adult subjects enrolled in the PK/PD substudy. Sputum samples will also be collected from all adolescent subjects who are enrolled in the study and are able to produce a sputum sample.
Note: The sputum sample collected for all subjects will be used for the substudy when substudy sample collection is scheduled at the same timepoint (no extra samples will be collected).
PD = pharmacodynamic; PK = pharmacokinetic.

APPENDIX 7. COMPARABLE NSAID DOSE LEVELS

Nonselective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Diclofenac potassium	50mg bid	50mg tid	50mg qid (in OA/RA only)
Diclofenac sodium	50mg bid	75mg bid	50mg qid or 100mg SR bid (in RA only)
Fenoprofen	200-300mg qid	600mg tid-qid	800mg qid
Flurbiprofen	50mg bid	50mg tid-qid	100mg tid
Ibuprofen	400mg tid	600mg tid-qid	800mg qid
Ketoprofen	25–50mg tid	75mg tid	IR =300mg/day (divide), SR =200mg/day
Naproxen	250mg tid	500mg bid	1250mg/day (divided)
Naproxen sodium	275mg tid	550mg bid	1375mg/day (divided)
Oxaprozin	600mg qd	1,200mg qd	1,200mg qd
Sulindac	150mg bid	200mg bid	200mg bid
Piroxicam	10mg qd	20mg qd	40mg per day (not indicated for OA or RA)
Partially-selective NSAIDs	**Low Dose**	**Medium Dose**	**High or Max Dose**
Etodolac	200mg tid	400mg bid	1,200mg max (IR or SR divided doses)
Meloxicam/Mobic	7.5mg qd	7.5mg qd	15mg qd
Nabumetone	1,000mg qd	1,000mg bid	2,000mg/day (qd or divided bid)
Cox-2 inhibitors	**Low Dose**	**Medium Dose**	**High or Max Dose**
Celecoxib/Celebrex	200mg qd	200mg bid	200mg bid

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release
*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.

Source: https://www.ncbi.nlm.nih.gov/sites/books/NBK65646/

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Version[a]**	**Date**
Global Amendment 3	6.0	09 AUG 2022
Global Amendment 2	5.0	07 DEC 2021
Global Amendment 1	4.0	12 MAR 2021
Original Protocol	1.0	31 JUL 2020

[a] Versions 2.0 and 3.0 are country-specific amendments.

Version 6.0, Global Amendment 3, (09 AUG 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes in Global Amendment 3 is to add collection of pharmacokinetic (PK) blood and pharmacodynamic (PD) sputum samples from all study subjects and to include the estimand framework.

Grammatical and typographical errors as well as internal inconsistencies have been corrected throughout the document.

A summary of major changes in this amendment compared to Global Amendment 2 is presented in the table below.

Revision	Rationale	Location of Revision
Added blood PK samples will be collected from all adult subjects and sputum PD samples from all newly enrolled adult subjects	To increase data availability for characterizing the PK and PD effects of brensocatib	• Section 3.1 • Table 5 • Section 8 • Appendix 5 • Appendix 6
Added study estimands for primary and secondary objectives, and updated statistical methods accordingly	To align with recommendations set forth in ICH E9(R1)	• Synopsis • Section 2 • Table 1 • Table 2 • Section 10
Added population PK analysis as an exploratory objective and added associated endpoint	To enhance brensocatib PK profiling	• Table 3

Revision	Rationale	Location of Revision
Clarified subjects from Ukraine will be replaced due to the war and that their data will be listed only and not included in the formal efficacy and safety analyses	Adverse impact of war on subject participation and data collection resulted in premature discontinuation of all active subjects; data handling is per agreement with FDA and EMA	• Section 4.2.3 • Section 10
Clarified the PK/PD substudy will not include subjects who are receiving cyclic antibiotics	Cyclic antibiotics impact NSP levels, which are measured in PD sputum and PD blood samples, and will introduce another variable beyond treatment or placebo to the interpretation of changes in NSPs	• Synopsis • Section 3.1 • Table 5, footnote 's' • Table 5, footnote 't' • Table 5, footnote 'u' • Section 7.2.2 • Section 8 • Section 8.2 • Section 10.1 • Appendix 5 • Appendix 6
Removed reference to evaluable subjects for the PK/PD and CT scan substudies	Subjects included in the analysis is defined by the analysis population and will be described in the respective analysis plans	• Synopsis • Section 3.1 • Table 5 , footnote 's' • Table 5 , footnote 'u' • Section 7.6.1 • Section 8 • Section 10.1
Clarified randomization will be enforced to have approximately (not at least) 30% of adult subjects with 3 or more prior PEs and to have approximately no more than 20% (not 25%) of subjects with eosinophil count $\geq 300/mm^3$ at Screening (not $>300/mm^3$ at Baseline)	To allow greater flexibility in randomization of subjects, to further limit the proportion of randomized subjects with eosinophilic inflammation, and to ensure eosinophil results will be available at randomization	• Synopsis • Section 1.5 • Section 3.1 • Section 5.2 • Section 10.1
Clarified lost to follow-up is after 3 reasonable efforts have been made and a certified letter has been sent	To provide standardized criteria for considering a subject lost to follow-up	• Section 4.2.2.3
Clarified subjects will be dosed at Visit 11 (Week 52)	To ensure standardized dosing at this visit	• Section 5.3

Revision	Rationale	Location of Revision
Removed requirement to document the time of informed consent in the eCRF and added the date and time of informed consent should be recorded in the source documents	Time informed consent is signed is not being captured in eCRF and to clarify proper documentation in the source documents	• Section 1.7.2
Removed requirement to document in IWRS the reason for unblinding, and clarified the reason for unblinding should be documented in source documents	IWRS does not collect reason for unblinding	• Section 5.6
Clarified drug storage, dispensing, and accountability procedures	To comply with EU CTA regulation (Annex 1, Section D and Title 51) in describing arrangements for tracing, storing, destroying, and returning study treatment	• Section 5.8 • Section 5.9 • Section 5.10
Clarified chronic treatment with "systemic" steroids (irrespective of the indication) is prohibited	Acute use of oral steroids is allowed; use of topical and inhaled steroids is also allowed	• Section 5.11.1
Updated to describe population PK analysis	To reflect current analysis plan	• Section 10.4.10
Added samples will be stored for up to 5 years (or longer if required by institution) for study-related evaluations and future research. Samples will not be used for genetic evaluations unless stated in separate consent. Samples may be used for further research with subject's consent. Clarified subjects may decide to not have their samples stored for a period of up to 5 years (not 2 years) beyond the duration of the study	To describe how stored samples may be used and to allow sufficient time for development of new analytical methodologies	• Section 13.4 • Section 13.5

CT = computed tomography; eCRF = electronic case report form; EU CTA = European Union Clinical Trial Application; FDA = Food and Drug Administration; EMA = European Medicines Agency; ICH = International Council for Harmonisation; IWRS = interactive web response system; NSP = neutrophil serine protease; PD = pharmacodynamic; PK = pharmacokinetic.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Version[a]**	**Date**
Global Amendment 2	5.0	07 DEC 2021
Global Amendment 1	4.0	12 MAR 2021
Original Protocol	1.0	31 JUL 2020

[a] Versions 2.0 and 3.0 are country-specific amendments.

Version 5.0, Global Amendment 2, (07 DEC 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes in Global Amendment 2 is to add the adolescent population (≥12 to <18 years of age) and to align with responses to health authority review comments.

Grammatical and typographical errors as well as internal inconsistencies have been corrected throughout the document.

A summary of major changes in this amendment compared to Global Amendment 1 is shown in the table below.

Revision	Rationale	Location of Revision
Added that approximately 40 adolescent subjects ≥12 to <18 years of age will be randomized in a 2:2:1 ratio to brensocatib 10 mg, brensocatib 25 mg, or placebo (no stratification applied) in participating countries and sites	At the recommendation of heath authority and to support marketing authorizations for brensocatib for the treatment of patients aged 12 years and older with NCFBE	• Synopsis • Section 1.3 • Section 3.1 • Section 5.2 • Section 10.1
Added brensocatib nonclinical toxicology data	Support safety of brensocatib dosing for >6 months in adolescent subjects	• Section 1.2.1
Added brensocatib dose justification for adolescent subjects	Indicate dose justification in adolescents based on height and weight distributions as well as simulated steady state AUC levels	• Section 1.3.2 • Section 1.3.4

Revision	Rationale	Location of Revision
Added enrollment criteria for adolescent subjects	Added informed consent/assent procedure, age range, weight, sputum sampling, and PE requirements to allow for enrollment of adolescent subjects	• Synopsis • Section 1.7.2 • Section 1.7.3 • Inclusion Criteria 1-3 • Inclusion Criteria 6-8 • Table 2
Added that adolescent subjects do not need to produce a sputum sample at Screening or any time during the study if they are unable to do so	Collecting sputum from young children is problematic as they find it difficult to expectorate	• Section 3.1 • Inclusion Criterion 6 • Inclusion Criterion 7 • Section 5.2 • Table 2 • Section 7.2 • Appendix 1
Clarified Secondary Endpoint #3 to indicate it is the change from Baseline in postbronchodilator FEV_1 at Week 52	Align with response to health authority review comment	• Synopsis • Section 2.2
Revised Secondary Objective/Endpoint #5 to indicate that QOL-B will be assessed in adult subjects	QOL-B will not be assessed in adolescent subjects	• Synopsis • Section 2.2 • Table 2 • Section 7.5.2
Revised Secondary Endpoint #6 to remove physical examination as a safety endpoint parameter	Physical examination data will not be summarized	• Synopsis • Section 2.2
Added Secondary Objective/ Endpoint #7 and deleted Exploratory Objective/ Endpoint #13	Brensocatib exposure will be evaluated in adults and adolescents using brensocatib concentration data at select time points (noncompartmental analyses will not be done)	• Synopsis • Section 2.2
Combined Exploratory Objectives/Endpoints #5 and #6 into a single Exploratory Objective/Endpoint #5	The effect of brensocatib compared with placebo on lung function will be evaluated by change from Baseline in pulmonary function parameters over the 52-week treatment period	• Section 2.3

Revision	Rationale	Location of Revision
Added Exploratory Objective/Endpoint #7 and associated assessments	The effect of brensocatib compared with placebo on the age-appropriate QOL-PCD domain scores over the 52-week treatment period will be evaluated in adolescent subjects with PCD	• Section 2.3 • Table 2 • Section 7.5.5
Combined Exploratory Objectives/Endpoints #9 and #10 into a single Exploratory Objective/Endpoint #9	Evaluate the effect of brensocatib compared with placebo on QOL-B domain scores over the 52-week treatment period in adult subjects	• Section 2.3
Added new Exploratory Objective/Endpoint #10	The PGI-S and PGI-C will be evaluated over the 52-week treatment period in adult subjects to confirm a meaningful change threshold for the QOL-B Respiratory Symptoms Domain endpoint at the recommendation of health authority	• Synopsis • Section 2.3 • Table 2 • Section 7.5.3
Revised Exploratory Objective/Endpoint #14 (formerly #15)	Add evaluation of neutrophil functions to blood PD evaluations and associated analyses in adult subjects	• Synopsis • Section 2.3 • Section 8.3 • Section 10.4.8
Removed exploratory objectives and endpoints from Synopsis	Exploratory objectives and endpoints are in Section 2.3 and are not required elements in the synopsis	• Synopsis • Section 2.3
Added additional randomization enforcement criteria and regional enrollment targets	Ensure enrolled study population is relevant to the NCFBE patient population	• Synopsis • Section 1.5 • Section 3.1 • Section 5.2 • Section 10.1
Added definition for individual subject completion	To define that an individual subjects is considered to have completed the study if he/she has completed all study visits including the Week 52 visit	• Section 3.4
Clarified Exclusion Criterion #15a	To specify subjects on antibiotics as chronic treatment should be on such treatment for at least 3 months prior to Screening (not enrollment)	• Exclusion Criterion 15a

Revision	Rationale	Location of Revision
Updated Exclusion Criterion #16 and align Section 5.11.1 with Exclusion Criterion #16	To clarify criterion by removing mention of oral budesonide and specify that oral steroids (any indication) are prohibited	• Exclusion Criterion 16 • Section 5.11.1
Revised Exclusion Criterion #19 to increase hepatic enzyme elevation thresholds for exclusion and to exclude Child-Pugh class C; Child-Pugh class B or C removed from Exclusion Criterion #30	At the recommendation of health authority to make the study as inclusive as possible and to avoid the potential for high drug exposure in study subjects	• Exclusion Criterion 19 • Exclusion Criterion 30
Clarified Exclusion Criterion #23	To specify receipt of any live attenuated vaccine within 4 weeks prior to Screening (not the first administration of brensocatib)	• Exclusion Criterion 23
Clarified Exclusion Criterion #25 to indicate subjects currently treated for periodontal disease are excluded and those undergoing standard dental care may be enrolled if said care is not related to periodontal disease (after Medical Director consultation)	Align with response to health authority review comment to make the study as inclusive as possible	• Exclusion Criterion 25 • Section 4.2.4 • Table 2
Clarified entry criteria for BMI and compliance with electronic diary entries are for adult subjects	BMI and electronic diary compliance criteria are not applicable to adolescent subjects	• Inclusion Criterion 3 • Exclusion Criterion 27
Clarified pregnancy testing requirements and overall pregnancy testing schedule for adolescent subjects	Adolescent females who reach menarche will be of child-bearing potential and clarified pregnancy testing should be performed according to the Schedule of Assessments or as required by local health authority	• Table 2 • Section 9.8
Added that all PEs will be adjudicated by an independent adjudication committee and specified that associated efficacy endpoints will be based on the adjudicated PEs	Determine if PEs fulfill the protocol definition and ensure the analyses will include those that fulfill the protocol-defined criteria; details will be provided in a separate charter	• Synopsis • Section 2 • Section 3.2 • Section 10.4.6.1.1

Revision	Rationale	Location of Revision
Updated the Schedule of Assessments	Updated all sections pertinent to the adolescent population; added health resource utilization; removed Baseline assessment for days of work/school missed; and changed the ±7-day window to start from Visit 3 (not Baseline, Visit 2)	• Table 2
Updated discontinuation procedures to specify the Investigator should contact the medical monitor to determine if the EOT CT assessment will be needed for subjects in the CT scan substudy	Subjects may not need to undergo the post-treatment scan if not in study long enough to provide meaningful data	• Section 4.2.2.1 • Section 4.2.2.2 • Table 2
Added subjects will be instructed to record each daily dose of study drug administered in an electronic dosing diary	To document dose administration for compliance assessments	• Section 5.3 • Section 5.5
Clarified that the BEST questionnaire will be completed by adult subjects and added retraining criteria	BEST will not be assessed in adolescent subjects and retraining criterion added to apply a quality standard	• Table 2 • Section 7.5.1
Clarified that EQ-5D-5L will be completed by all subjects (adult and adolescent)	EQ-5D-5L will also be assessed in adolescent subjects	• Table 2 • Section 7.5.4
Deleted BEST diary card, EQ-5D-5L sample, and QOL-B sample from appendices	The instruments will be provided separately to the Investigator, IRB/IEC, and health authority, if required	• Section 15
Clarified that the 12-lead ECG should be performed before PFT when scheduled at the same visit	Mitigate any effect of PFT testing on ECG recording	• Table 2 • Section 9.4
Updated language regarding follow-up of AEs/SAEs	Distinguish between procedures and timing for AE follow-up versus SAE follow-up	• Section 9.10 • Section 9.12
Added protocol-defined PEs should not be reported at AEs unless they fulfill a seriousness criterion and clarified PEs do not fall into the other infections AESI category	Protocol-defined PEs are collected as efficacy endpoints via the eCRF	• Section 9.10.1 • Section 9.10.3.3

Revision	Rationale	Location of Revision
Clarified that self-monitoring for periodontitis/gingivitis will be performed by adult subjects; the Investigator will monitor adolescent subjects	Ensure adolescents are properly monitored for periodontitis/ gingivitis during the study	• Section 9.10.3.2
Added SAE reporting contact information	Provide e-mail and back-up fax number to report SAEs	• Section 9.11.2
Clarified that database lock will occur when 1620 adult subjects complete the 52-week treatment period or discontinue from the study; primary efficacy and safety analyses will include all adult and adolescent data collected up to the database lock	Align with response to health authority recommendation to include all available adolescent data in the primary analysis	• Synopsis • Section 10
Updated sample size and power calculations for adolescent subjects	Provide the basis for a sample size of approximately 40 adolescent subjects	• Synopsis • Section 10.1
Clarified that the PK/PD and CT scan substudies will enroll evaluable adult subjects and added the respective definition for an evaluable subject. Added that PK and sputum PD samples will be collected from all adolescent subjects.	To clarify the population enrolled in each substudy and to ensure a sufficient number of evaluable subjects will be enrolled.	• Synopsis • Section 3.1 • Section 7.6.1 • Section 8 • Section 10.1
Updated the statistical analysis sets and analytical methods	To align with changes in study objectives/endpoints and align with responses to health authority review comments	• Section 10.2 • Section 10.4

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (12 MAR 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary driver for the changes in the protocol amendment is to address health authority responses and to provide clarifications of study procedures.

Grammatical and typographical errors were corrected throughout the document.

A summary of major changes in this amendment, compared to the original protocol, is shown in the table below.

Revision	Rationale	Location of Revision
Added Inclusion Criterion #11	Require male subjects to use a condom to provide protection against potential fetal exposure	• Inclusion Criterion #11
Updated Inclusion Criterion #4	To clarify that the CT scan should be high-resolution	• Inclusion Criterion #4 • Table 2, footnotes "g" and "h" • Section 3.1 • Section 7.8.1 • Section 9.3
Updated definition of contraception in Inclusion Criterion #9	Defined "highly effective contraception" and clarified the role Investigator and designee in explaining contraception to subjects	• Inclusion Criterion #9
Updated Exclusion Criterion #4	Added Centers for Disease Control (CDC) definition of "current smoker"	• Exclusion Criterion #4
Added Exclusion Criterion #35	Included hypersensitivity to brensocatib and/or excipients as exclusion	• Exclusion Criterion #35
Updated Exclusion Criterion #16	To add exceptions to chronic use of oral steroids	• Exclusion Criterion #16
Updated Exclusion Criterion #27	To clarify the criterion	• Exclusion Criterion #27
Updated the type of pregnancy test to be performed at Baseline (Day 1)	To change the test from a serum test to a urine test, allowing a more rapid results readout	• Section 9.8 • Table 2 footnote "i"

Revision	Rationale	Location of Revision
Updated risks and mitigation strategies	To add information on how AESIs were determined for the study	• Section 1.4.2
Updated text for the AESI of "Other Infections"	To add further clarification	• Section 9.10.3.3
Updated text for the informed consent and regulatory compliance procedure	To clarify the procedure	• Sections 1.7.2, 1.7.3
Updated the early discontinuation procedures	To clarify the procedure	• Section 4.2.2.2
Updated the rescreening procedures	To clarify the procedure	• Section 4.2.4
Updated film-coating information for all study drugs	Correction of film-coating information for all study drugs	• Section 5.1
Updated text on matters not to be discussed by study personnel and subjects	To avoid suppressing communication of safety issues	• Section 5.1.2
Added text to describe study drug administration	To clarify that the study drug tablets must not be broken or chewed	• Section 5.1.3
Added text on dose interruption	To clarify that dose interruption due to safety issues is allowed	• Section 5.1.3.1
Updated text to clarify unblinding procedures	To clarify that unblinding is the sole responsibility of the Investigator	• Section 5.1.5
Updated concomitant medications	To add vaccinations and diagnostic tests to the list	• Section 5.2
Updated text on the prohibited use of chronic steroids and live attenuated vaccines	To add clarification on exceptions and duration of the prohibited medications	• Section 5.3
Updated text on sputum sample shipping procedure	To update the number of days sputum samples can be stored before shipping	• Section 7.2.2
Updated the volume of blood drawn for PD samples	Laboratory specification change	• Section 3.1 • Section 8.4.2 • Table 2 footnote "r"
Updated text on the initiation of study	To clarify that approval from the Health Authority, where applicable, is needed prior to enrollment	• Section 13.6

Revision	Rationale	Location of Revision
Revised description of QOL-B questionnaire, updated footnote "n" for Schedule of Assessments and Procedures, and updated Appendix 5 – QOL-B	Correction: QOL-B was modified to remove the demographics page; the procedure was further clarified	• Sections 3.1, 7.6 • Table 2 footnote "n" • Appendix 5
Updated Appendix 2 – Calculation of Bronchiectasis Severity Index	To clarify that Hospital admission is due to bronchiectasis exacerbation	• Appendix 2
Updated Appendix 7 on Investigator's actions when potential Hy's law criteria are met	To clarify the process	• Appendix 7

Document History		
Document	**Version**[a]	**Date**
Global Amendment 1	4.0	12 MAR 2021
Original Protocol	1.0	31 JUL 2020

[a] Ver 2.0 provided a country-specific amendment for Denmark; Ver 3.0 provided country-specific amendments for Belgium, Japan, Portugal, Canada, Latvia, and France.