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

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STATISTICAL ANALYSIS PLAN

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AESI	adverse event of special interest
AA	Airway-Artery
ANC	Absolute neutrophil count
ATC	Anatomical Therapeutic Class Level
BDRM	Blind data review meeting
BEST	Bronchiectasis Exacerbation and Symptom Tool
BEST-CT	Bronchiectasis Scoring Technique for Computed Tomography
BLQ	Below the limit of quantification
BSI	Bronchiectasis Severity Index
CAR	Censored-at-random
CatG	Cathepsin G
CEC	Clinical Endpoint Committee
CID	Clinically important deterioration
CMQ	Customized MedDRAQuery
CNAR	Censored-not-at-random
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
DMC	Data Monitoring Committee
DRR	Data review report
EAR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQoL-5 Dimension-5 Level Questionnaire
ER	Emergency room

Abbreviation	Term
$FEF_{(25-75\%)}$	Forced expiratory flow between 25% and 75% of forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FMQ	FDA Medical Query
FVC	Forced vital capacity
gCV%	Geometric coefficient of variation percentage
GM	Geometric mean
H_{01}	Primary Hypotheses 1
H_{02}	Primary Hypotheses 2
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
IP	Investigational Product
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
LS	Least squares
MAR	Missing-at-random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
MNAR	Missing-not-at-random
MRC	Medical Research Council
n	Number of non-missing observations
NC	Not calculable
NE	Neutrophil elastase
NCFBE	Non-cystic fibrosis bronchiectasis
NSP	Neutrophil serine protease
PD	Pharmacodynamic
PE	Pulmonary exacerbation
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
I-C	Patient Global Impression of Change

Abbreviation	Term
PCSA	Potentially Clinically Significant Abnormalities
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/pharmacodynamic
PPD	Patients Pocket Depth
$ppFEV_1$	Percent predicted forced expiratory flow in 1 second
PR3	Proteinase 3
PT	Preferred Term (MedDRA)
QD	Once daily
QoL-B	Quality of Life Questionnaire – Bronchiectasis
QoL-PCD	Quality of Life Questionnaire – Primary Ciliary Dyskinesia
SD	Standard deviation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMQ	Standardized MedDRAQuerycm
SOC	System Organ Class (MedDRA)
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report (CSR) for study INS1007-301.

The reader is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for a participant to complete the participation in this study.

The SAP is intended to be aligned with the protocol. However, the SAP may contain more details or other types of analyses. Differences in descriptions or explanations provided in the study protocol and this SAP, are discussed in Section 13. The SAP is based upon the following documents:

- Clinical Study Protocol (CSP) (Global) Amendment 4, Version 7, dated 13 Feb 2024,
- Electronic Case Report Form (eCRF) Version 14, dated 21 Sep 2023.

Details pertaining to the scope of analyses for Data Monitoring Committee (DMC) review are provided in the DMC SAP.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and unblinding. Any analyses not described herein performed subsequent to unblinding will be considered post hoc and exploratory.

2. STUDY OBJECTIVES AND ESTIMANDS

The treatment effect of brensocatib will be evaluated using the On-Study Estimands primarily; supported using the On-Investigational Product (IP) and On-Treatment Estimands. The treatment regimen in the On-Study Estimand is the randomized assignment to IP irrespective of discontinuation or modifications to standard of care. The On-Study Estimand provides a pragmatic assessment of brensocatib's effectiveness. The treatment regimen for the On-IP estimand is the randomized IP irrespective of modifications to standard of care. The treatment regimen for the On-Treatment Estimand is the randomized IP plus standard of care without addition of new chronic antibiotics during the treatment period or modifications to chronic antibiotics taken at baseline. The On-Treatment estimand describes brensocatib's efficacy.

Note, chronic treatment with antibiotics is permitted for all Estimands if such treatment was initiated at least 3 months prior to Screening. For this study, standard of care is equal to being on a chronic course of antibiotics without any changes in dose nor administration route at baseline. About 20% of participants are on chronic treatment with antibiotics.

The On-Treatment assessment of efficacy is considered supplementary, and will be important in describing the risk:benefit and cost-effectiveness. For this Estimand, the intercurrent event (ICE) of initiation of a new chronic antibiotic during the 52-week treatment period will be defined as any antibiotic intake for more than 28 days other than for the treatment of a concurrent pulmonary exacerbation. Discontinuation from a baseline chronic antibiotic during the 52-week treatment period is also an ICE for the On-Treatment estimand as this can impact the assessment of efficacy. Further, participants randomized but not treated will be excluded from any statistical analysis and data tabulation.

The Composite Estimand will be utilized as a supplementary assessment of responder status for whether participants are exacerbation free over the 52-week treatment period. Participants who experience ICEs associated with treatment failure (i.e., addition of a new chronic antibiotic during the treatment period, early discontinuation of IP due to lack of efficacy, early discontinuation of IP due to a treatment-related adverse event (AE), or death due to Non-Cystic Fibrosis Bronchiectasis [NCFBE]) will be considered as "non-responder" for the endpoint. ICEs of early discontinuation of IP for other reasons will be handled using the Treatment Policy strategy per the International Council for Harmonisation (ICH) E9(R1) Addendum.

2.1. Primary Objective and Estimands

The primary objective is to evaluate the effect of brensocatib at 10 mg and 25 mg compared with placebo on the adjudicated Annualized Rate of PEs.

The primary and supplementary Estimands for the primary objective including their attributes (i.e., the variable, the population level summary, the treatment regimen, and the strategies per the ICH E9(R1) Addendum to be implemented for addressing the study's relevant ICEs) are presented in the Table 1 below. The population attribute for these Estimands is participants with NCFBE.

Table 1: Primary Endpoint and Estimands

Variable	Population Level Summary	Estimand Name	Treatment Regimen	ICEs/Strategy	Section
Annualized Rate of PEs	Rate Ratio	Primary: On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP/ Treatment Policy Modification to standard of care/ Treatment Policy	8.2.1
		Supplementary: On-Treatment	Standard of care + randomized IP	Early discontinuation from randomized IP/ While On-Treatment Modification to standard of care/ While On-Treatment	8.2.5
		Supplementary: On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP/ While On-Treatment Modification to standard of care/ Treatment Policy	8.2.5

2.2. Secondary Objectives and Estimands: Efficacy

The secondary objectives are to evaluate the effect of brensocatib compared with placebo for the Estimands described in Table 2. Unless otherwise noted, the population attribute for the secondary Estimands is participants with NCFBE.

Table 2: Secondary Endpoints and Estimands: Efficacy

Variable	Population Level Summary	Estimand Name	Treatment Regimen	ICEs/Strategy	Section
Time to first PE	Hazard Ratio	Primary: On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.3.1.1
		Supplementary: On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment Modification to standard of care / Treatment Policy	8.3.1.3
Responder status for exacerbation free	Odds Ratio	Primary: On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.3.2.1
		Supplementary: Composite	Standard of care + randomized IP	Early discontinuation from randomized IP for lack of efficacy, tolerability or death due to NCFBE / Composite (Impute non-responder) Early discontinuation from randomized IP for other reasons / Treatment Policy	8.3.2.2

				Early discontinuation from standard of care / Treatment Policy Addition of chronic antibiotics/ Composite (Impute non-responder)	
Change in post-bronchodilator forced expiratory volume in 1 second (FEV_1) at Week 52	Mean Difference	Primary: On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.3.3.1
		Supplementary: On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment Modification to standard of care / Treatment Policy	8.3.3.3
Annualized Rate of severe PEs	Rate Ratio	Primary: On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.3.4.1
		Supplementary: On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment Modification to standard of care / Treatment Policy	8.3.4.3
Change from Baseline in Quality of Life Questionnaire – Bronchiectasis	Mean Difference	Primary: On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.3.5.1
		Supplementary: On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment	8.3.5.3

(QoL-B) Respiratory Symptoms Domain Score at Week 52*				Modification to standard of care / Treatment Policy	

* The population for Change in QoL-B Respiratory Symptoms Domain Score at Week 52 will be adult participants with NCFBE

2.3. Secondary Objectives: Safety

In participants with NCFBE, the secondary safety objectives are to evaluate the safety and tolerability of brensocatib. For details refer to protocol Section 2.2.

2.4. Secondary Objectives: Pharmacokinetics

In participants with NCFBE, the pharmacokinetic (PK) objective is to evaluate brensocatib exposure in adults and adolescents. For details refer to protocol Section 2.2.

3. STUDY DESIGN

3.1. Summary of 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 doses of brensocatib compared with placebo in participants with NCFBE. Approximately 1,620 adult participants will be randomized in a 1:1:1 ratio to 3 treatment arms (540 participants per treatment arm) to receive brensocatib 10 mg QD, brensocatib 25 mg QD, or matching placebo QD for 52 weeks (refer to Section 3.3). For this study, the adolescent population is defined as participants ≥12 to <18 years of age who have had at least 1 PE in the prior year. Approximately 40 adolescent participants 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.

After baseline, participants will return to the study site for in-clinic visits at Weeks 4, 16, 28, 40, 52 (end of treatment [EOT]), and 56 (end of study [EOS]), during which they will be assessed for PEs and undergo clinical laboratory tests, vital signs measurement, and assessment by means of questionnaires (BEST, QoL-B, PGI-S/PGI-C, QoL-PCD, and EQ-5D-5L). In addition, collection of the days of work and/or school missed due to PE will occur. Telephone visits will occur at Weeks 10, 22, 34, and 46, during which collection of AEs, concomitant medications, smoking status, periodontal complaints, questionnaires (as mentioned above), and assessment for occurrence of PEs will occur. At Visit 11 (Week 52/EOT) participants 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), participants will complete all protocol-specified assessments and EOS procedures.

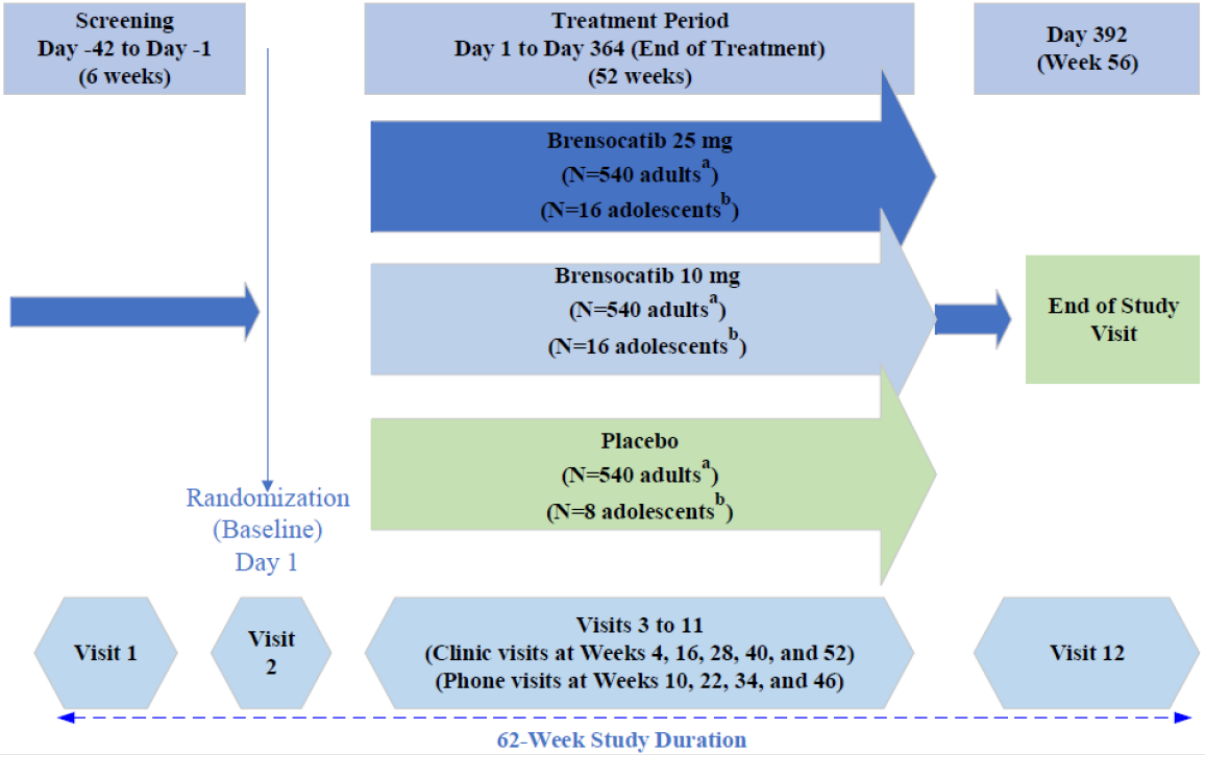
The study will include a pharmacokinetic/pharmacodynamic (PK/PD) substudy comprising approximately 300 adult participants who sign a substudy informed consent form (ICF) and who are not receiving cyclic antibiotics at Baseline. In a separate PD sub-study, approximately 40 adult participants will have blood samples collected for evaluation of neutrophil functions as well as NE, CatG and PR3 concentrations in blood. This will occur in a very limited number of sites with laboratory capabilities, and a specific substudy ICF for adults will be provided. PK and sputum PD samples will be collected from all adolescent participants. The sampling schedule will be the same as that for adults in the PK/PD substudy. In addition, PK samples and PD sputum samples will be collected from some of the participants in the main study after Amendment 6 was in effect.

The schedule of sample collection for each of the aspects of the substudy is detailed in Appendix 5 and Appendix 6 of the CSP.

The study will also include a CT scan substudy with approximately 225 adult participants. This substudy will include 2 study-specific high-resolution CT scans to be conducted at the Screening Visit and the Week 52 Visit.

The procedures and assessments conducted at each study visit are provided Table 5 of the CSP ("*Schedule of Assessments and Procedures*"). Please refer to Figure 1 for a schematic diagram of the study design.

Figure 1: Study Design



[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

All participants are encouraged to stay in the study regardless of study treatment discontinuation.

3.2. Sample Size Determination

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 for adult participants over the 52-week treatment period (≥18 years and ≤85 years of age [inclusive] at Screening). Assuming the annualized PE rate in the placebo arm is 1.2 events with a negative binomial distribution with dispersion of 1, a total of 1,620 adult participants randomized in a 1:1:1 ratio to brensocatib 10 mg, brensocatib 25 mg and matching placebo, respectively, will yield 90% overall power to demonstrate that at least 1 dose of brensocatib is superior to placebo under the Truncated Hochberg procedure (overall alpha = 0.01; two-sided test; truncation fraction = 0.9). The ratio of exacerbation rate is assumed to be 0.70 (brensocatib over placebo) between any of the brensocatib treatment arms and placebo after 52 weeks of treatment.

The PK/PD substudy is targeted to enroll approximately 300 participants; the sample size is based on clinical considerations and participant numbers for the PK study.

The CT substudy is targeted to enroll approximately 225 adult participants; the sample size is based on clinical considerations and participant numbers for the CT study.

In addition, approximately 40 adolescent participants will be enrolled in a 2:2:1 randomization scheme (16:16:8) to minimize exposure to placebo treatment. The sample size 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 contract research organization (CRO). The sponsor believes this proposed sample size will provide an adequate description of the safety profile of brensocatib in this age group and assessment of brensocatib exposure and offer the possibility to observe directional trends in terms of efficacy.

3.3. Randomization

After meeting all inclusion criteria and none of the exclusion criteria, adult participants will be randomized through an interactive web response system (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 participants per treatment arm). Randomization will be stratified based on region (North America, Europe, Japan, and the Rest of the World), sputum sample 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.

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 participants with 3 or more prior PEs, to have no more than 20% of participants older than 75 years of age, to have approximately no more than 20% of participants with eosinophil count in peripheral blood ≥300/mm^3 at Screening, and to have no more than 20% of participants with COPD as a comorbidity.

Approximately 40 adolescent participants 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 participants per treatment arm, respectively). Adolescent participants will not be required to produce a sputum sample at the Screening Visit if they are unable to provide. There will be no stratification for adolescent participants. To allow inclusion of adolescent data into the statistical analysis, the stratification factor covariates will be derived as follows:

- Exacerbation frequency in last 12 months from BSI form
- Colonization status from the sputum sample collection form. This is the IHMA source information for the colonization status. If the sputum result is missing, but the BSI colonization category is present then the value comes from BSI form[1]. If both IHMA source and BSI colonization category are missing, presence of Pseudomonas Aeruginosa will be considered as 'Negative' for the analysis.

[1] The BSI form has three outcomes for colonization status: "*Not Colonized*", "*Chronic Colonization*", and "*P. Aeruginosa Colonization*". For the analysis the outcomes "Chronic colonization" and "*P. Aeruginosa Colonization*" will identify presence of Pseudomonas Aeruginosa.

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

DMC members may have access to unblinded data when necessary. Refer to Section 4.3 of this document for more details.

Unblinding is only to occur in the case of participant emergencies, for the primary database lock, and at the conclusion of the study.

4. PLANNED ANALYSES

4.1. Interim Analysis

No interim efficacy analyses will be conducted for this study.

4.2. Final Analyses

The planned primary database lock is based on the time when the targeted 1620 adult participants (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 (excluding participants from Ukraine and participants from site USA065) will be included in the primary efficacy and safety analyses for the Clinical Study Report (CSR). Additional data collected between the primary database lock and the last adolescent participant completing the last visit (final database lock) will be summarized in a CSR addendum.

4.3. DMC Monitoring

Periodic review of data for the purpose of safety will be conducted by a DMC; details are described in a separate DMC charter and DMC SAP, together with details regarding safety summaries and listings.

5. ANALYSIS SETS

Participants from Ukraine and participants from US site USA065 will not be included in the formal efficacy and safety analyses of ASPEN data. As part of the Screened Analysis Set (as defined below), they will be tabulated in the "Analysis Set" data (see Section 7.1). All data will be listed separately.

5.1. Screened Analysis Set

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

Technical note: Participants with non-missing ICF date will be included.

5.2. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set comprises all participants who were randomized, excluding participants from Ukraine and participants from site USA065. This set will be analyzed using the treatment to which the participant was randomized, regardless of the treatment actually received.

Participants in the screened analysis set with a randomization number will be included. Participant-IDs starting with "UKR-" will be excluded, and participant-IDs starting with "USA065-" will be excluded.

5.3. Safety Analysis Set

The Safety Analysis Set comprises all participants who were randomized and received at least 1 dose of brensocatib or placebo and will exclude participants from Ukraine and participants from site USA065. The Safety Analysis Set will be analyzed using the actual treatment received. Derivation of participants' actual treatment is detailed in Section 6.4.2.

Randomized participants who received at least 1 dose of IP will be included.

5.4. Pharmacodynamic Analysis Sets

The PD Analysis Set comprises participants who have consented to participate in the PD substudy, in adolescent cohort and in the main study, have received at least 1 dose of study drug, and have at least 1 predose and 1 postdose measurement of biomarkers, and will exclude participants from Ukraine and participants from site USA065. The PD Analysis Set will be analyzed using the actual treatment received.

This study has two sources for PD parameters. This is why the PD analysis set is further differentiated between the below analysis sets.

The Blood PD Analysis Set comprises participants who have consented to participate in the PD Blood substudy, have received at least 1 dose of study drug, and have at least 1 pre-dose and 1 post-dose measurement of blood biomarkers, and will exclude participants from Ukraine and participants from site USA065. Blood PD will not be collected for adolescents.

The Sputum PD Analysis Set comprises participants who have received at least 1 dose of study drug and have at least 1 predose and 1 postdose measurement of sputum biomarkers, and will exclude participants from Ukraine and participants from site USA065.

PD biomarkers are NE, CatG, and PR3, also referred to as neutrophil serine proteases (NSPs). Participants in these Analysis Sets will be used for all PD summaries and statistical analyses.

5.5. Pharmacokinetic Concentration Analysis Set

The PK Concentration Analysis Set comprises participants who have consented to participate in the PK substudy, in adolescent cohort and in the main study, have received at least 1 dose of brensocatib, and have at least 1 post-dose plasma concentration of brensocatib, excluding participants from Ukraine and participants from site USA065. Participants will be classified according to actual treatment received regardless of the treatment group to which they were randomized.

5.6. CT Scan Analysis Set

The CT Scan Analysis Set comprises participants who have both baseline and post-baseline CT measurement data, excluding participants from Ukraine and participants from site USA065. The CT Scan Analysis Set will be analyzed using the actual treatment received.

Participants with non-missing consent date to participate in the CT substudy and with non-missing baseline and post-baseline CT data available will be included in this analysis set for all CT summaries and statistical analyses.

6. GENERAL STATISTICAL CONSIDERATIONS

The statistical software package SAS® Version 9.4 (SAS Institute, Cary, NC, USA) will be used to perform all analyses and to summarize data.

6.1. General

All summaries will be provided by treatment group, if not stated otherwise (see Section 6.4.2 below). Some presentations will describe specific populations, and this will be evident in each output as necessary.

Descriptive statistics for continuous variables will be calculated at scheduled visits (nominal time points for PK concentration) and will include the number of participants in the treatment group/dose level of the respective Analysis Set (N in column header of the table), the number of non-missing observations (n), arithmetic mean, standard deviation (SD), CV%, median, minimum, and maximum. For NSP concentrations and percent change from baseline in blood and sputum, mean, SD, CV%, median, minimum, maximum will be determined. For brensocatib plasma concentrations and PD results, the geometric mean (GM) with 95% CI and geometric coefficient of variation -percentage (gCV)%, and the number of observations below limit of quantification (BLQ) will also be reported. The GM will be derived by calculating the arithmetic mean of the log-transformed observations and then back-transforming the mean by exponentiation. The gCV% will be calculated as: 100*sqrt (exp [variance of the log-transformed values] - 1). GM -and gCV% will only be calculated for quantifiable values above 0 (if at least 1 value are less than 0, e.g., for PD parameters, no GM and gCV% will be displayed but left empty). Listings will present the data in its original format.

Categorical variables will be summarized by counts and by percentage of participants in the corresponding categories. The number of participants in the treatment group/dose level of the respective Analysis Set (N in column header of the table) and the number and percentage of non-missing observations in each category will be provided. A category including missing assessments may be added if appropriate. Footnotes will specify the denominator used for the percentages.

In case of mis-randomization to incorrect strata, participants will be analyzed according to the strata into which they were randomized.

Data from unscheduled visits will not be used in summaries, except for the derivation of baseline (see Section 6.4.3).

If not specified otherwise, reported p-values and confidence intervals will be 2-sided. P-values greater than or equal to 0.001 will be presented to three decimal places. P-values less than 0.001 will be presented as “<0.001”. Confidence intervals will be presented to one more decimal place than the estimate.

All efficacy and safety data that have already been collected from the Ukraine or from site USA065 will be listed only and not included in the formal efficacy and safety analyses of ASPEN data. Listings will be produced for AE, demography and baseline characteristics, and IP exposure. The Ukraine and site USA065 listings will remain separate from the rest of the

study data for ease of review. Note: The originally planned sample size of 1,620 participants will not include participants from Ukraine or participants from site USA065.

6.2. Considerations for Constructing Estimands

Analysis of the On-Study Estimands will be conducted in the ITT Analysis Set (see Section 5.2) in which all observed data will be included regardless of whether the participants remain on randomized IP. This Estimand will be considered the Primary Estimand and utilizes the Treatment Policy strategy for ICEs (see Section 2). Analyses of the On-IP and On-Treatment Estimands will be conducted using the ITT Analysis Set for efficacy endpoints.

For all On-Study Estimands for the primary and secondary endpoints in the multiple testing procedure, tipping point sensitivity analysis will only be conducted if the main results are statistically significant.

A blinded data review meeting (BDRM) will be conducted to review the definition of analysis sets, the assignment of participants into the analysis sets, as well participants meeting criteria for ICEs of the study Estimands (see Section 2). A data review report (DRR) will be prepared and signed prior to database lock and unblinding to document participant's assignment into analysis sets and agreed actions for participants meeting any ICE criteria prior to database lock and unblinding. Any incorrect treatment assignments determined subsequent to database lock and unblinding will be included in the DRR minutes as an addendum.

Analysis details are presented in Section 9.

6.2.1. Identification of ICEs

The following subsections will describe the two ICEs defined for this study.

If both ICEs occur at the same date, e.g., early discontinuation from randomized IP and modification from standard of care at the same date, the early discontinuation from randomized IP will be prioritized. Within standard of care the discontinuation from standard of care will be prioritized over addition of new chronic antibiotics.

6.2.1.1. Early Discontinuations from Randomized IP

Early discontinuation from randomized IP will be identified through the eCRF "*End of treatment*". A participant will be considered as early discontinued from randomized IP if the question "*Did the subject complete the planned treatment per protocol?*" was answered with "*No*".

The date entered for "*Last dose date*" will be used as date of ICE onset.

6.2.1.2. Modifications to Standard of Care: Addition/Discontinuation Chronic Antibiotics

The addition of a new chronic antibiotic treatment or discontinuation from standard of care (i.e., baseline chronic antibiotics) is defined as any change of the chronic antibiotics that was stable at baseline. For additional evaluation, this ICE may be broken down into the subtypes:

"*Initiating new Chronic Antibiotics*", "*Adding a new Chronic Antibiotic to the Existing Chronic Antibiotic Regimen*", and "*Changing Chronic Antibiotics*" given their derivation in the sub-sections below.

Participants discontinuing from standard of care with no replacement, e.g., no new use of antibiotics, will be counted separately. Any changes in dose or frequency of the same chronic antibiotics within 7 days will NOT be counted as discontinuation from standard of care as it is considered as continuation of the standard of care therapy. Example, if chronic antibiotic A which was present at baseline stopped and restarted within 7 days with the same or a modified dose or frequency, the chronic antibiotic A will not be considered as discontinuation from standard of care.

Special care will be taken for partially reported dates of standard of care therapy. Please refer to Section 6.9.2 for further details.

Any standard of care stopped at the same date as IP administration stop date will not be considered as an ICE.

Due to its nature this data is complex and requires additional methods. Please refer to Appendix M for further details.

6.2.1.2.1. Initiating new Chronic Antibiotic Treatment

Initiation of chronic antibiotics will be identified through entries in eCRF "*Prior and concomitant medications*". World Health Organization (WHO) Drug dictionary codes provided in Appendix K will be used to identify start of new chronic antibiotics. The start date of the new chronic antibiotic must be on or after the date of randomization, and at least 7 days from the end of the previous therapy, if applicable. The date entered for "*Start date*" will be used as date of ICE onset.

Note: it is expected that first IP administration is administered at the date of randomization (refer to Section 6.4.2). In circumstances where the date of first IP is not equal to the date of randomization, the date of first IP administration will be used as reference date. Hence, the start date of the new chronic antibiotic must be on or after the date of first IP administration. This rule applies to the below two sub-sections, too.

6.2.1.2.2. Adding a New Chronic Antibiotic to the Existing Chronic Antibiotic Regimen

Adding a new chronic antibiotic to an existing chronic antibiotic regimen will be identified through entries in eCRF "*Prior and concomitant medications*". WHO Drug dictionary codes provided in Appendix K will be used to identify addition of new chronic antibiotics. This ICE subtype applies only in cases where the participant has already (at least) one record for taking chronic antibiotics at time of randomization. The start date of the new chronic antibiotic must be on or after the date of randomization.

The date entered for "*Start date*" will be used as date of ICE onset.

6.2.1.2.3. Changing Chronic Antibiotics

Changing existing chronic antibiotics will be identified through entries in eCRF "*Prior and concomitant medications*". WHO Drug dictionary will be used to identify existing and new chronic antibiotics. This ICE subtype applies only in cases where:

- the participant has already (at least) one record for taking chronic antibiotics at time of randomization,
- the start date of the new antibiotic is on or after the date of randomization,
- the existing chronic antibiotic has a stop date entered and the same has not been restarted within 7 days after the stop. Change in dose or frequency of the same chronic antibiotics will be considered as restart,
- the start date of the new antibiotic is within 7 days commencing the stop date of the existing chronic antibiotic.

The date entered for "*End date*" of the existing chronic antibiotic will be used as date of ICE onset.

6.2.2. Time to (first) ICE

Time to first ICE in days will be calculated as

$$Time\ to\ (first)\ ICE\ (days) = start\ date\ of\ first\ ICE - date\ of\ reference + 1.$$

Participants who do not have an ICE during the 52-Week treatment period will be censored at time of EOT.

The date of reference will be the date of first IP administration, if not stated otherwise. If a participant was randomized but not treated with IP, the participant will be censored at study day 1 (day of randomization).

6.3. Multiple Comparisons and Multiplicity Adjustment

The study has 3 treatment groups (brensocatib 25 mg, brensocatib 10 mg, and placebo), 1 primary endpoint, and 5 secondary efficacy endpoints. The annualized rate of PEs is the primary efficacy endpoint. The time to first pulmonary exacerbation, the responder status for being exacerbation free over the 52 weeks, the change in post-bronchodilator FEV_1 at Week 52, the annualized rate of severe PEs, and the change in QoL-B respiratory symptoms domain score at Week 52are the secondary efficacy endpoints. The overall type I error rate control will focus on the comparisons of the two brensocatib doses relative to placebo for the primary endpoint and all these five secondary endpoints.

In this study, the enhanced mixture-based gatekeeping procedure (Kordzakhia et al, 2018) is 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 12 null hypotheses ($H_1, H_{2,\ldots,}H_{12}$) listed in Table 3 below. 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 $\alpha = 0.01$.

6.3.1. Families and Hypotheses

With the 6 efficacy variables, 6 families are constructed, respectively, as Family 1 through Family 6, which are indexed from 1 to 6 according to the order of clinical importance, as shown in Table 3. This table lists the null and alternative hypotheses by family for each pairwise comparison in the Multiplicity Adjustment procedure. Each family has two null hypotheses (one for each of the brensocatib doses in comparison to placebo).

Table 3: Families (Endpoint/Dose) and Hypotheses in Multiplicity Adjustment

Null and Alternative Hypotheses by Family

Brensocatib 25 mg vs Placebo	**Brensocatib 10 mg vs Placebo**
Family 1: Annualized Rate of PEs (Rate Ratio)	
$\boldsymbol{H_1}: \frac{\lambda_H}{\lambda_P} = \mathbf{1}$ vs $H_{11}: \frac{\lambda_H}{\lambda_P} \neq 1$	$\boldsymbol{H_2}: \frac{\lambda_L}{\lambda_P} = \mathbf{1}$ vs $H_{21}: \frac{\lambda_L}{\lambda_P} \neq 1$
Family 2: Time to First PE (Hazard Ratio)	
$\boldsymbol{H_3}: \frac{h_H}{h_P} = \mathbf{1}$ vs $H_{31}: \frac{h_H}{h_P} \neq 1$	$\boldsymbol{H_4}: \frac{h_L}{h_P} = \mathbf{1}$ vs $H_{41}: \frac{h_L}{h_P} \neq 1$
Family 3: Responder Status for Exacerbation Free (Odds Ratio)	
$\boldsymbol{H_5}: \frac{\theta_H}{\theta_P} = \mathbf{1}$ vs $H_{51}: \frac{\theta_H}{\theta_P} \neq 1$	$\boldsymbol{H_6}: \frac{\theta_L}{\theta_P} = \mathbf{1}$ vs $H_{61}: \frac{\theta_L}{\theta_P} \neq 1$
Family 4: Change in Post-Bronchodilator FEV_1 at Week 52 (Mean Difference)	
$\boldsymbol{H_7}: \boldsymbol{\mu^{(F)}_H - \mu^{(F)}_P = 0}$ vs $H_{71}: \mu^{(F)}_H - \mu^{(F)}_P \neq 0$	$\boldsymbol{H_8}: \boldsymbol{\mu^{(F)}_L - \mu^{(F)}_P = 0}$ vs $H_{81}: \mu^{(F)}_L - \mu^{(F)}_P \neq 0$
Family 5: Annualized Rate of Severe PEs (Rate Ratio)	
$\boldsymbol{H_9}: \frac{\lambda_H}{\lambda_P} = \mathbf{1}$ vs $H_{91}: \frac{\lambda_H}{\lambda_P} \neq 1$	$\boldsymbol{H_{10}}: \frac{\lambda_L}{\lambda_P} = \mathbf{1}$ vs $H_{101}: \frac{\lambda_L}{\lambda_P} \neq 1$
Family 6: Change in QoL-B Respiratory Symptoms Domain Score at Week 52 (Mean Difference)	
$\boldsymbol{H_{11}}: \boldsymbol{\mu^{(Q)}_H - \mu^{(Q)}_P = 0}$ vs $H_{111}: \mu^{(Q)}_H - \mu^{(Q)}_P \neq 0$	$\boldsymbol{H_{12}}: \boldsymbol{\mu^{(Q)}_L - \mu^{(Q)}_P = 0}$ vs $H_{121}: \mu^{(Q)}_L - \mu^{(Q)}_P \neq 0$

Note: The subscript H to parameters $(\lambda, \theta, \mu^{(F)}, \mu^{(Q)})$ denotes High Dose (Brensocatib 25 mg), the subscript L denotes Low Dose (Brensocatib 10 mg), and a subscript P denotes Placebo.

6.3.2. Mixture-based gatekeeping procedure

The proposed mixture-based gatekeeping procedure includes the following features (Dmitrienko and Tamhane, 2011 and 2013, and Kordzakhia et al., 2018):

- A truncated version of the Hochberg test will be used in Family 1. The gatekeeping procedure will proceed to the next family even if only one comparison is significant (a single hypothesis is rejected) in Family 1.
- The Bonferroni test will be used in Families 2-5. The gatekeeping procedure will proceed to the next family even if only one comparison is significant (a single hypothesis is rejected) in the current family.
- The Hochberg test will be used in Family 6.

The test statistics within Families 1 and 6 follow a bivariate normal distribution with a positive correlation induced by the common placebo arm. Under these conditions, the positive dependence condition (MTP2 condition), which guarantees local Type I error rate control within these families, is met (Sarkar and Chang, 1997; Sarkar, 1998).

The closed testing representation is constructed based on pre-specified truncation parameters γ_k, for Family k $(= 1,2,3,4,5,6)$. The above proposed procedure uses a testing algorithm based on $\gamma_1 = 0.9$ for Family 1, $\gamma_k = 0$ for Family $k(= 2,3,4,5)$, and $\gamma_6 = 1$ for Family 6. This representation will be used to compute multiplicity-adjusted p-values for the 12 individual null hypotheses, $H_1, H_2, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}, H_{11}, H_{12}$.

The testing algorithm utilizes the closure principle and specifies the decision rule for each intersection hypothesis in the closed family associated with the 12 null hypotheses. The closed family contains $2^{12} - 1 = 4095$ intersections of the original null hypotheses. Define an arbitrary index set as $I \subseteq \{1,2,3,4,5,6,7,8,9,10,11,12\}$. Let $H(I)$ denote an arbitrary intersection hypothesis from the closed family, which is associated with the index set I. A local p-value, also known as the intersection p-value, will be computed for the intersection hypothesis $H(I)$ as shown below using the raw p-values for the individual null hypotheses. The raw p-values are denoted by p_1 through p_{12}.

To ensure that the procedure is consistent with the logical restrictions among the null hypotheses, the corresponding restrictions need to be imposed on the hypotheses within each intersection. These restrictions ensure, for example, that the null hypothesis H_3 cannot be rejected if the null hypothesis H_1 is not rejected (H_3 will be automatically accepted if H_1 is not rejected). Let I^* denote the restricted index set which accounts for the logical relationships among the null hypotheses within the intersection hypothesis $H(I)$. For example, if the intersection hypothesis is given by $H_1 \cap H_2 \cap H_3$, the original index set is $I = \{1, 2, 3\}$. After the logical restrictions are imposed, the restricted index set is $I^* = \{1, 2\}$ since the hypothesis H_3 cannot be rejected if the null hypothesis H_1 is not rejected.

It is easy to show that, for any intersection hypothesis $H(I)$, there can be at most two indices left in the restricted index set I^*. Because of this, it is sufficient to consider the following two cases:

Case 1. Suppose that there are two indices in the restricted index set I^* that are denoted by i and j, i.e., $I^* = \{i, j\}$.

a. If the corresponding hypotheses are included in the same family, the following subcases will be considered:

- The Hochberg test is used in Families 1 and 6. Thus, the local p-value for this intersection hypothesis is constructed using the Simes approach, i.e., the local p-value is given by $p(I) = \min\big(2\min(p_i, p_j), \max(p_i, p_j)\big)$, where $I^* = \{1, 2\}$ for Family 1 and $I^* = \{11,12\}$ for Family 6.
- Since the Bonferroni test is used in Families 2,3, 4, and 5, the local p-value for this intersection hypothesis is constructed using the Bonferroni approach, i.e., the local p-value is given by $p(I) = 2\min(p_i, p_j)$.

b. If the corresponding hypotheses are included in two different families, let i denote the index corresponding to the more important family, the following subcases will be considered:

- If the index i is equal to 1, the local p-value for this intersection hypothesis is given by $p(I) = 2\min(p_i/(1+\gamma_i), p_j/(1-\gamma_i))$.
- If the index i is greater than 1, the local p-value for this intersection hypothesis is given by $p(I) = 2\min(p_i, p_j)$.

Case 2. Suppose that there is only one index in the restricted index set I^*, denoted by i, i.e., $I^* = \{i\}$. In this case, the local p-value for the intersection hypothesis is simply given by $p(I) = p_i$.

The resulting local p-values for the intersection hypotheses in the closed family will be utilized for computing the multiplicity-adjusted p-values for the 12 null hypotheses. Specifically, consider the multiplicity-adjusted p-value for the null hypothesis H_i, $i = 1, \ldots 12$, which is denoted by $\tilde{p}_i$. This adjusted p-value is defined as the maximum over the local p-values for all intersection hypotheses that include H_i, i.e.,

$$\tilde{p}_i = \max_{i \in I} p(I).$$

A null hypothesis will be rejected if its adjusted p-value is less than or equal to a pre-defined significance level. The formulae of adjusted p-values of individual null hypotheses are provided in Appendix J.

In case Brensocatib is worse than Placebo in terms of point estimator in one or more of the 12 hypotheses, all 12 two-sided p-values will be converted to one-sided p-values when applying the mixture-based gatekeeping procedure, and the adjusted one-sided p-values will be converted back to adjusted two-sided p-values.

6.4. General Definitions and Derivations

6.4.1. Definition of IP Completion and Study Completion

A participant will be considered as completing the IP if the question "*Did the subject complete the planned treatment per protocol?*" on the EOT form is answered with "*Yes*".

A participant will be considered as completing the study if the question "*Did the subject complete the study?*" on the EOS form is answered with "*Yes*".

6.4.2. Date of First / Last IP intake, Treatment Display in Data Tabulations, and Actual Treatment

Administration of IP is collected daily using an electronic diary. Participants are not able to enter missed doses retrospectively, while the very first dose may not be recorded. Participant's date of attending Visit 2 is used as the First Dose Date (SCH_VS dataset [Visit Dataset]) as participants will receive their initial dose at the site. A date of first dose will be assigned only if records for IP administration were reported fulfilling the condition "*Did you take your study medication today?*" = "Yes" (for at least one record) in the drug administration form ("*Dose Administration*" within the Patient Cloud folder of the CRF). Participants attending Visit 2 but without any records in "Dose Administration" fulfilling the condition will be considered as not being treated with randomized IP.

The "*Last dose date*" entered in the EOT form will be used to determine the date of last administration of randomized IP.

If not stated otherwise, tabulations will be presented by treatment groups and overall using the following labelling throughout all displays:

- Brensocatib 10 mg;
- Brensocatib 25 mg;
- Placebo;
- All Participants (applicable study population summaries only, unless stated otherwise [see Section 6.9]),
- Pooled Brensocatib (applicable for all safety tables, unless stated otherwise).

The participant's actual treatment for the Safety, Pharmacodynamic, PK Concentration, and CT Scan Analysis Sets will be derived from exposure data. The Kit ID dispensed by the IRT and actual kit ID used will be recorded. If a participant's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a participant receives a study treatment that is different from the assigned treatment, then the following rule will apply:

- the actual treatment group will be set to placebo, brensocatib 10 mg or brensocatib 25 mg depending on the most common administered dose, regardless of the randomized treatment.

6.4.3. Baseline Definition, Change from Baseline

According to Table 5 of the CSP ("*Schedule of Assessments and Procedures*"), the second visit (V2) is defined as "*Baseline*". However, the definition of the "*Baseline*" which is used to

derive any changes of assessments during study conduct, e.g., laboratory parameters, depends on the timing of the first IP administration and can therefore be different from Baseline/Day 1/Visit 2. Therefore, unless otherwise stated, for the purpose of analysis baseline value is the last non-missing value prior to or at the date of the first dose of IP, considering also unscheduled visits. For participants who do not receive IP during the study, baseline is defined as the latest, non-missing collected value on or before Study Day 1.

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline is calculated as:

$$visit\ value - baseline\ value.$$

If either the baseline or visit value is missing, the change from baseline will be set to missing as well.

For summaries, whenever baseline is presented, the above baseline definition is used. That is, the baseline summary presented is in general not the summary of the (CSP defined) Baseline/Day 1 visit. Screening values will be listed but not summarized. Throughout the document, Baseline (capital B) refers to the visit Baseline/Day 1; baseline (lower case b) refers to the values derived using the baseline definition above.

6.4.4. Multiple Assessments

If a participant has more than one numeric record for a specific parameter of interest at a specific visit and/or timepoint for any reason (but the same source, e.g., central lab), the latest of that specific data at that visit and/or timepoint will be considered in summary tables, unless otherwise stated.

If a result will be assessed by local and central laboratories, central assessment will be used for reporting purposes.

Data from all assessments (local and central; scheduled and unscheduled), including multiple assessments, will be included in listings.

6.4.5. Calculation of Study Day

In general, the date of randomization and the date of first IP administration should coincide, both expected to occur at Visit 2, Baseline. However, discrepancies between these dates may arise which leads to two reference dates to be defined in this study:

- On-Study Estimands: the reference date is the date of randomization and will be used to calculate Study Day for efficacy measures, e.g., time to event.
- On-IP and On-Treatment Estimands: the reference date is the very first date of IP administration and will be used to calculate Study Day for safety measures, e.g., to assess whether an AE is treatment-emergent or not, additional sensitivity and supplementary analysis.

Study Day for On-Study Estimands

If the date of interest occurs on or after the date of randomization, then (efficacy) Study Day will be calculated as

$$(date\ of\ interest - date\ of\ randomization) + 1.$$

If the date of interest occurs prior to the date of randomization, then (efficacy) Study Day will be calculated as

$$(date\ of\ interest - date\ of\ randomization).$$

There is no efficacy Study Day 0.

Study Day for On-IP and On-Treatment Estimands

If the date of interest occurs on or after the date of initial IP administration, then the (safety) Study Day will be calculated as

$$(date\ of\ interest - date\ of\ first\ IP\ administration) + 1.$$

If the date of interest occurs before the date of initial IP administration, then the (safety) Study Day will be calculated as

$$(date\ of\ interest - date\ of\ first\ IP\ administration).$$

There is no safety Study Day 0.

6.4.6. Calculation of Pack-Years

Number of pack-years smoked will be calculated as:

$$pack\_years = (packs\ smoked\ per\ day) * (years\ of\ smoke).$$

The following list defines the transformation required to calculate a single pack for the various substances. Note, 20 cigarettes define a single pack.

- Pipe: 1 pipe a day equals to 2.5 cigarettes per day
- Cigar: 1 cigar a day equals to 4 cigarettes per day
- Cannabis / marijuana: 1 joint/pipe a day equals to 2.5 cigarettes per day

6.4.7. Durations, Exposure Days, Follow-up Time, Compliance

Duration

A duration between one date (*date1*) and another later (or the same) date (*date2*) is calculated using the following formula and presented by one decimal place, if not stated otherwise:

- Duration (days) = *date2* – *date1* + 1
- Duration (weeks) = duration (days) / 7
- Duration (months) = duration (days) / (365.25 / 12)
- Duration (years) = duration (days) / 365.25

The duration on study will be calculated as number of days between date of randomization and EOS visit:

$$duration\ on\ study\ (days) = date\ of\ EOS - date\ of\ randomization + 1.$$

The duration of individual IP exposure will be calculated as number of days between date of first intake of IP and the date of last intake of IP (see Section 6.4.1).

$$exposure\ duration\ (days) = date\ of\ last\ IP\ intake - date\ of\ first\ IP\ intake + 1.$$

The above calculation does not account for protocol-allowed dose interruptions.

The duration of treatment will be evaluated as follows:

$$(actual)\ treatment\ duration\ (days) = actual\ treatment\ duration\ (days) - number\ of\ missed\ IP\ due\ any\ reasons.$$

Participant's Follow-up Time or Observation Time

The individual follow-up time / observation time in years will be calculated using the following formula:

$$follow-up\ time\ (years) = \frac{date\ of\ EOS - date\ of\ first\ IP\ intake}{365.25}.$$

For participants ongoing at time of primary analysis, e.g., adolescents, the date of cut-off will be used as date of EOS.

Compliance

Participants will be required to bring all their used and unused IP supplies to in-clinic study visits during the treatment period or, if the visit is being conducted virtually, have all used and unused study drug supplies available to be accounted for. Compliance will be calculated by considering the number of dispensed and returned pills in the eCRF as follows:

$$compliance\ (\%) = \frac{number\ of\ doses\ taken}{number\ of\ doses\ expected} * 100\ .$$

The number of doses expected is the number of doses a participant is "potentially" able to take. Missed doses for any reason, or any doses after treatment discontinuation will not be considered as "expected", hence excluded.

Missed IP or missed dose will be recorded in the participant's diary and eCRF. If participant's missed dose or days when dose was missed is unknown, the number of dispensed and returned pills in the eCRF will be evaluated to determine participants' number of doses missed. If the amount returned is missing in the eCRF, a worst-case approach will be used, and the returned number of tablets will be set to be equal to the dispensed number of tablets. This means that the participant took no dose from a particular dispensed kit.

6.4.8. Definition of Prior, Concomitant and Post-Treatment Medications and Procedures

Prior, concomitant, and post-treatment medications (procedures) will be coded using the WHO Drug Dictionary. Procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications (or procedures) are defined as medications (or procedures) that started prior to the first administration of randomized IP. Concomitant medications (or procedures) are defined as medications (or procedures) taken between first administration of randomized IP and last randomized IP plus 28 days. Post-treatment medications are defined as medications taken during the post treatment period where post treatment period starts after last randomized IP plus 28 days. A medication that starts prior to the first administration of randomized IP but continues after the first administration and ends on or before last randomized IP plus 28 days is classified as both prior and concomitant medication. If the end

date of a medication is partially missing (or fully missing / unknown), and the possible interval for the end date includes the date of the first administration of randomized IP, the medication will be considered concomitant.

A medication (or procedure) that starts after the last dose of randomized IP plus 28 days is not considered concomitant but post-treatment. A medication (or procedure) that starts before last dose of randomized IP but continues after last dose of randomized IP plus 28 days is considered as concomitant and post-treatment.

6.4.9. Data Re-allocation for Early Discontinued Participants

Data collected at multiple visits (spirometry, smoking status, vital signs, and laboratory data) recorded at the EOT visit (Week 52, Visit 11) for early discontinued participants will be re-allocated. Re-allocation will depend on the actual date of the EOT visit and the closest expected (scheduled) visit date.

For example, if the last visit performed before the EOT visit is Visit 4, the data recorded at the EOT visit will be re-allocated to Visit 5 or 6 depending on the date of the study termination visit. If the study termination visit was performed less than 7 days after the preceding visit, e.g., if the EOT visit was performed in the same visit window as defined in Section 6.5, data other than PEs/AEs/SAEs/AESIs recorded at the EOT visit will not be re-allocated and they will be excluded from the statistical analysis, summary tables and figures. For each assessment, only the visits at which the assessment was scheduled per CSP will be considered for re-allocation. This means that vital signs and laboratory data can be re-allocated to Visits 3, 5, 7 and 9 only. Visit windowing as defined in Section 6.5 will be considered for allocation of data.

Assessments completed every 2nd week, e.g., PGI-S, PGI-C, and QoL-B, will not be re-allocated.

6.5. Visit Windowing

The CSP defines for each of the study visits from Visit 3 (Week 4, Day 28) to EOS (Visit 12, Week 56, Day 392), a ±7-day visit window. However, the visit schedule may not be followed due to various reasons such as patients travel arrangements, etc. The goal is to use all available data such as data from unscheduled visits to minimize missing data at scheduled, nominal visits. Therefore, programmatic visit windowing will be applied to analysis datasets preparation.

Based on the actual visit date, the actual measure will be allocated to the specific visit using visit intervals as specified in Table 4. After all observations have been evaluated following the defined visit intervals, it may appear that an interval has multiple (valid) observations for the same assessment within the same scheduled, nominal visit. For the analysis, one of these observations will be used while the selection will follow the below rules (in the sequential order given):

- Select the observation closest to the target Study Day,
- Select the latter observation if 2 observations are equally close to the target Study Day.

Table 4: Visit Windowing

Scheduled Visit (Nominal Visit)	Scheduled Visit Day (Study Day)	Visit Intervals
Screening		<= -1
Day 1	1	1
Week 4	28	2 to 49*
Week 10	70	50 to 91
Week 16	112	92 to 133
Week 22	154	134 to 175
Week 28	196	176 to 217
Week 34	238	218 to 259
Week 40	280	260 to 301
Week 46	322	302 to 343
Week 52	364	344 to 378
Week 56	392	>=379

*Note: Visit windowing will not be applied to assessments completed every day, or every 2 weeks. Refer to PRO assessments as described in Section 6.7.5. Further, in cases where the first IP was administered after day of randomization, visit windowing will not overrule assignment of baseline record and windowing will not be applied. As an example, consider a participant with date of randomization at 22-Jul but IP administration was at 24-Jul. Data reported at date of IP administration would have analysis date equal to 3 (date – date of randomization + 1). If visit windowing applied, participants would not have a baseline. Therefore, visit windowing will not be applied for those records who fulfill the constraint of the baseline.

6.6. Reporting of Data After Early Discontinuation of IP

All participants who discontinued IP early are encouraged to stay in the study for continued assessments following the same study procedures until the EOS. Reasons for early IP discontinuation will be recorded. If a participant withdraws consent from continued monitoring, the EOS visit will be completed.

The purposes for collecting these data are to permit full efficacy data ascertainment per the ITT principle in accordance with the On-Study estimand and to allow continual monitoring of participant safety for the 4-week follow-up period after IP discontinuation.

Reporting rules for data collected after early discontinuation of IP are outlined for each data type (efficacy, safety, pharmacokinetic, pharmacodynamic, etc.) per the corresponding estimand, specifically the ICE handling strategy.

Safety data that are excluded from treatment emergent period, i.e., data collected after the 4-week follow-up post early discontinuation of IP, will be reported separately and will include basic summaries of:

- AE, SAEs and AESIs, (non-treatment emergent)
- Laboratory
- Concomitant medication.

Other collected safety data will be listed.

6.7. Definitions and Derivations of Efficacy Variables

6.7.1. Pulmonary Exacerbations

Only exacerbation events that meet the protocol definition of PE diagnosis confirmed by an independent adjudication committee will be included into the analysis (refer to Section 10.4.6.1.1 of the CSP for further details and the Clinical Endpoint Committee [CEC] Charter).

The calculation of the time at risk as well the inclusion of data into the analysis depends on the underlying Estimand. Refer to Table 5 for further details. In general, participants' time at risk will be the time on study excluding the time during exacerbations.

Table 5: PEs to be included into the analysis and time at risk based on Estimand

Estimand Name	PEs included in the analysis	Time at risk
On-Study (Primary)	All observed PEs up to Week 52 who meet the protocol defined criteria of PE diagnosis	Date of Week 52 visit / early study discontinuation[2] – date of randomization + 1 minus the sum of number of days the participant experiences exacerbation events that meet the protocol definition of PE diagnosis (end date of the PE – start date of the PE + 1). Refer to Section 6.7.1.1 for further instructions in case of combined PEs.
On-Treatment and On-IP (Supplementary)	All observed PEs up to end of IP / first ICE onset who meet the protocol defined criteria of PE diagnosis	Date of last IP intake / date of first ICE onset – date of first IP intake + 1 minus the sum of number of days the participant experiences exacerbation events that meet the protocol definition of PE diagnosis prior to the first ICE (end date of the PE – start date of the PE + 1). Refer to Section 6.7.1.1 for further instructions in case of combined PEs.

Rules defined above will not be applied to the analysis of PEs as AEs, e.g., not fulfilling protocol-defined criteria (see Section 7.1 of the CSP).

If a PE is ongoing at EOS, the PE end date will be EOS date, given query for resolution failed. If the PE end date is longer / after the EOS date, then the PE end date will be set to the

[2] Note: The Week 52 visit is the EOT visit per CSP and the date is determined through the eCRF form "*V11 (EOT or E/D)*". The date of last IP administration will be determined through eCRF form "*End of Treatment*" as indicated in Section 6.4.2. Participants who complete IP and the Week 52 visit as per protocol the on-study and on-treatment estimand will select the same data for analysis. Participants who discontinue from IP early, the date of Week 52 visit will be calculated as MINIMUM(date of EOS, date of randomization + 363) to match the scheduled date of Week 52 to keep similarity across participants discontinuing the study early.

EOS date to calculate the time at risk. Participants ongoing at time of primary analysis, e.g., adolescents, the date of cut-off will be used as PE end date.

6.7.1.1. Combining of PEs / Episodes

A minimum of 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. Any exacerbations that occur less than 2 weeks from the end date of the previous exacerbation will be considered the same exacerbation and the following rules will be applied:

- the maximum severity between the two will be applied for the combined event,
- the start date of the earlier event will be used as start date for the combined event,
- the end date of the latest event will be used as end date for the combined event,
- the duration of the combined event will be calculated as end date of the combined PE – start date of the combined PE + 1,
- the time at risk of combined events will be adjusted by the duration of the start and end date of the combined event as detailed in the previous bullet
- the question "*Does this Pulmonary Exacerbation meet the criteria of a Serious Adverse Event?*" will show "Yes" if at least one of the combined events reported "Yes"
- symptoms will be uniquely combined, e.g., if "Increased cough" was reported for both individual events, the combined event will have "Increased cough" reported once, otherwise reported symptoms will be concatenated,
- antibiotics use for the individual events will be reported for the combined event as recorded without any modification.

Note: If two or more PEs were combined into a single exacerbation, the single exacerbation will be analyzed.

6.7.1.2. Annualized Rate of PEs

For the primary analysis, the response variable is the number of PEs the participant experiences up to Week 52, with the time at risk of experiencing a PE included as offset in the model.

PEs with a start date that occurs after a participant's discontinuation from IP while remaining in the study for follow-up will be managed according to the Estimand. The time at risk will be adjusted, too (see Table 5).

For descriptive summaries, the crude Annualized Rate of PEs is calculated as:

$$Annualized\ Rate\ of\ PEs = \frac{Number\ of\ PEs}{Time\ at\ Risk} * 365.25,$$

where number of PEs and Time at Risk is following the definitions described in Table 5.

6.7.1.3. Duration of PEs

The duration of PEs (days) will be calculated as

$$Duration\ PE\ (days) = end\ date\ of\ PE - start\ date\ of\ PE\ + 1.$$

6.7.1.4. Days Hospitalized for Adjudicated PEs per Person-Year

Hospitalization for adjudicated PEs will be identified through the CRF "*Hospitalization visits log*" and the reason for hospitalization given as "*Indication under study*". The recorded admission and discharge dates will be used to calculate participants number of days hospitalized, e.g.,

$$duration\ (days) = date\ discharge - admission\ date + 1.$$

For missing admission or discharge dates, the duration of hospitalization will not be calculated.

The number of days hospitalized due to adjudicated PEs per person-year is calculated as total number of days hospitalized due to indication under study by the total time on treatment:

$$(days\ hospitalized\ for\ indication\ under\ study\ per\ person\_year)_{trt} = \frac{\sum(days\ hospitalized\ for\ indication\ under\ study)_{i,trt}}{\sum time\_on\_treatment_{i,trt}(years)},$$

where i describes the participant of $trt \in$ {brensocatib 10mg, brensocatib 25mg or placebo}. The total time on treatment in days will be calculated for each treatment (trt) by pooling all patients time on treatment in years together.

6.7.1.5. Days of Absence from Work/School Related to Adjudicated PEs per Patient Year Over the 52 Week Treatment period

To get the number of days absent from work/school the CRF "*Missed work/school YN*" will be used. Data will only be gathered if both questions "*Is the subject currently working or attending school?*" and "*Has the subject missed any days of work/school since the last visit due to reasons related to bronchiectasis symptoms?*" are answered with "*Yes*".

Missed days of work/school will be identified through the CRF "*Missed work/school log*". The recorded number of days in the CRF field "*How many days?*" will be used. The number of days absent from work/school will be linked to the adjudication outcome. Days of absence will be summarized only.

The number of days missed work/school due to adjudicated PEs per year is calculated as total number of days missed by the total time on treatment:

$$(days\ missed\ per\ person\_year)_{trt} = \frac{\sum(days\ missed)_{i,trt}}{\sum time\_on\_treatment_{i,trt}(years)},$$

where i describes the participant of $trt \in$ {brensocatib 10mg, brensocatib 25mg or placebo}. The total time on treatment in days will be calculated for each treatment (trt) by pooling all patients time on treatment in years together.

6.7.1.6. Time to First Pulmonary Exacerbation

The time to first exacerbation event confirmed through adjudication will be calculated as

$$Time\ to\ first\ PE\ (days) = CEC\ assessed\ onset\ date\ of\ first\ PE - date\ of\ reference^{*} + 1.$$

*For the On-Study Estimand the date of reference will be the date of randomization, while for the On-Treatment Estimand the date of reference will be the date of first IP administration (see Sections 6.4.1 and 6.7).

Participants who do not have a PE confirmed through adjudication during the 52-week treatment period or for whom the first PE is recorded beyond Week 52 visit will be censored at the date of Week 52 (or at the date of EOS for participants early discontinued from study) visit for the On-Study Estimand and at the date of last IP intake or the date of first ICE onset for the On-Treatment Estimand. Participants randomized but not treated will not be analyzed for the On-Treatment Estimand but censored at the day of randomization.

6.7.1.7. Reporting of Pulmonary Exacerbations in Study Months

The onset date of a PE will determine the assignment into the "Study Months". The reference date for On-Study estimand will be the date of randomization. Technical instructions given below:

```
if 0 le (pulmdt - randdt) + 1 le 1 * 30.4375             then pexm1 = 1;  else pexm1 = 0;
if 1 * 30.4375 lt (pulmdt - randdt) + 1 le 2 * 30.4375   then pexm2 = 1;  else pexm2 = 0;
if 2 * 30.4375 lt (pulmdt - randdt) + 1 le 3 * 30.4375   then pexm3 = 1;  else pexm3 = 0;
if 3 * 30.4375 lt (pulmdt - randdt) + 1 le 4 * 30.4375   then pexm4 = 1;  else pexm4 = 0;
if 4 * 30.4375 lt (pulmdt - randdt) + 1 le 5 * 30.4375   then pexm5 = 1;  else pexm5 = 0;
if 5 * 30.4375 lt (pulmdt - randdt) + 1 le 6 * 30.4375   then pexm6 = 1;  else pexm6 = 0;
if 6 * 30.4375 lt (pulmdt - randdt) + 1 le 7 * 30.4375   then pexm7 = 1;  else pexm7 = 0;
if 7 * 30.4375 lt (pulmdt - randdt) + 1 le 8 * 30.4375   then pexm8 = 1;  else pexm8 = 0;
if 8 * 30.4375 lt (pulmdt - randdt) + 1 le 9 * 30.4375   then pexm9 = 1;  else pexm9 = 0;
if 9 * 30.4375 lt (pulmdt - randdt) + 1 le 10 * 30.4375  then pexm10 = 1; else pexm10 = 0;
if 10 * 30.4375 lt (pulmdt - randdt) + 1 le 11 * 30.4375 then pexm11 = 1; else pexm11 = 0;
if 11 * 30.4375 lt (pulmdt - randdt) + 1 le 12 * 30.4375 then pexm12 = 1; else pexm12 = 0;
if 12 * 30.4375 lt (pulmdt - randdt) + 1                 then pexm13 = 1; else pexm13 = 0;
```

The variable `PULMDT` describes the PE onset date and the variable `RANDDT` the date of randomization.

6.7.2. Responder Status for Exacerbation-Free over the 52-Week Treatment Period

For the On-Study Estimand, a participant will be defined as "*Responder*" / "*Non-responder*" based on exacerbation events that are confirmed through adjudication over the 52-week treatment period.

In order, to be a "*Responder*" participants must:

- complete 52-Weeks on study, AND
- have no exacerbation event that meets the protocol definition of PE diagnosis confirmed by an independent adjudication committee during the 52-Weeks.

If a participant has at least one PE confirmed through adjudication during the 52-Week study period, the participant will be classified as "*Non-responder*".

For participants who discontinue the study prior to Week 52 without having experienced a PE confirmed through adjudication, their responder status will be imputed based on the observed data model (see Section 8.3.2.1).

For the Composite Estimand, the above criteria must be met, at a minimum, in order to be classified as "*Responder*". However, participants meeting one of the below criteria will be considered as "*Non-responder*", given no PE was observed prior to:

- Early discontinuation from randomized IP for the below reasons:
  - Death due to NCFBE (to be investigated through the AE page)
  - Lack of efficacy
  - Tolerability; defined as discontinuation from randomized IP due to an AE which is deemed to be related to the randomized IP by the investigator; cases will be identified through the AE eCRF by looking for action="DRUG WITHDRAWN", relationship="RELATED"
- Addition of chronic antibiotics over the 52-Week Treatment Period

Early discontinuation from randomized IP for other reasons will follow the Treatment Policy strategy.

6.7.3. Change from Baseline in Pulmonary Function Test Parameters and Rate of Change in FEV_1 (Pre- and Post-bronchodilator)

Prebronchodilator and postbronchodilator pulmonary function test (PFT) parameters will be determined by spirometry. To ensure quality control, all spirometry's are reviewed independently to ensure that they meet ATS/ERS acceptability criteria (see CSP Section 7.3). Only those spirometry tracings determined to be acceptable, or borderline will be used, based on the best effort selected by ERT per spirogram. If more than one best effort was recorded for each of multiple screening visits, the last record will be used for the analysis. Optional PFT assessments will be excluded from all analysis but listed only. They will not be considered for the determination of baseline.

The baseline will be derived as the most recent pulmonary function test parameter assessment (separately for prebronchodilator and postbronchodilator) prior to first administration of randomized IP using measurements determined as best effort and selected for the analysis, e.g., the last measurement in case of multiple screening visits.

The absolute change from baseline at Week X will be calculated as (definition shown for FEV_1 only but applies the same for all pulmonary function test parameters):

$$FEV_{1,Change\ from\ Baseline\ at\ Week\ x} = FEV_{1,Week\ x} - FEV_{1,Baseline}.$$

Percentage Change from baseline in FEV_1

The percentage change in from baseline in FEV1, separately for prebronchodilator and postbronchodilator, will be calculated as

$$FEV_{1,change\ from\ baseline}(\%) = \left(\frac{FEV_{1,Week\ x}}{FEV_{1,Baseline}} - 1\right) * 100.$$

6.7.4. Annualized Rate of Severe Pulmonary Exacerbation Events that Meet the Protocol Definition of PE Diagnosis

A severe exacerbation event that meets the protocol definition of PE diagnosis is defined as a PE requiring IV antibacterial drug treatment and/or hospitalization and must also be confirmed as severe through the event adjudication process.

The same derivation rules will be used as for Annualized Rate of PEs (see Section 6.7.1.2) with the exception, the PEs will be limited to severe PEs only.

6.7.5. Patient-Reported Outcomes

Patient-Reported Outcomes data will be collected via an electronic patient-reported outcome device (ePRO device). Age-dependent questionnaires, e.g., QoL-PCD, will remain throughout the study regardless of a change in participant's age.

6.7.5.1. Windowing

QoL-B, PGI-S, and PGI-C will be completed every 2nd week. To allocate data correctly, bi-weekly periods are defined in Table 6, where Day 1 is the day of randomization.

Table 6: Bi-Weekly Windowing for PRO assessments

Period	Bi-Weekly (Days)*	Target Date for Assessment	Label in data tabulations
Baseline	Day 1		Baseline
1	Day 2 – Day 22	Day 15	Week 2
2	Day 23 – Day 36	Day 29	Week 4
3	Day 37 – Day 50	Day 43	Week 6
4	Day 51 – Day 64	Day 57	Week 8
5	Day 65 – Day 78	Day 71	Week 10
6	Day 79 – Day 92	Day 85	Week 12
7	Day 93 – Day 106	Day 99	Week 14
8	Day 107 – Day 120	Day 113	Week 16
9	Day 121 – Day 134	Day 127	Week 18
10	Day 135 – Day 148	Day 141	Week 20
11	Day 149 – Day 162	Day 155	Week 22
12	Day 163 – Day 176	Day 169	Week 24
13	Day 177 – Day 190	Day 183	Week 26
14	Day 191 – Day 204	Day 197	Week 28
15	Day 205 – Day 218	Day 211	Week 30
16	Day 219 – Day 232	Day 225	Week 32
17	Day 233 – Day 246	Day 239	Week 34
18	Day 247 – Day 260	Day 253	Week 36
19	Day 261 – Day 274	Day 267	Week 38
20	Day 275 – Day 288	Day 281	Week 40
21	Day 289 – Day 302	Day 295	Week 42
22	Day 303 – Day 316	Day 309	Week 44
23	Day 317 – Day 330	Day 323	Week 46
24	Day 331 – Day 344	Day 337	Week 48
25	Day 345 – Day 358	Day 351	Week 50

26	Day 359 – Day 372	Day 365	Week 52
27	Day 373 – Day 386	Day 379	Week 54
28	>=Day 387	Day 393	Week 56

* Day 1 is the date of randomization. Baseline is defined as the most recent assessment on or before day 1.
The assessment date is the scheduled date based on a bi-weekly interval.

6.7.5.2. QoL-B (Adults only)

QoL-B will be completed every 14 days. Windowing will be performed as given in Table 6. In case of multiple QoL-B assessments falling into an interval, the observation closest to the target study day will be selected; or the latter observation if 2 (or more) observations are equally close to the target study day.

Calculation of QoL-B domain scores is detailed in Appendix A.

6.7.5.3. Bronchiectasis Exacerbation and Symptoms Tool (Adults only)

The BEST Diary will be completed every day and a score will be calculated for each daily entry. BEST Diary Baseline Score is defined as average of BEST Diary daily scores from screening to Study Day 1 (inclusive)[3]. The daily change from Baseline in BEST score over the 52-week treatment period will be calculated for each participant as the individual daily change from baseline. In addition, a BEST Diary Score (overall post-baseline) will be calculated, defined as the average of all the non-missing BEST Diary daily score for a given participant post-baseline.

BEST data will also be averaged over 4-week periods in a table and figure.

Calculation of the BEST score is detailed in Appendix E.

6.7.5.4. Patient Global Impression of Severity scale (PGI-S) in Adults

PGI-S will be completed every 14 days. Adult participants enrolled under global CSP amendment 2 and later will complete the PGI-S on an electronic device where validated translations are available in the local language. Participants enrolled prior to global CSP amendment 2 will not complete the PGI-S.

The PGI-S assesses how a participant perceives their overall severity over the past week. The response options of the PGI-S are scored using a 5-point scale: 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe. Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

No additional scoring will be performed for the PGI-S. If PGI-S was assessed more than once within 2 weeks, the observation closest to the target Study Day will be selected; or the latter observation if 2 observations are equally close to the target Study Day. All data will be listed.

[3] Note: Participants can be rescreened up to 2 times with the sponsor's medical director approval (refer to Section 4.2.4 of the CSP). For the determination of baseline all data reported will be used including data from previous screening periods.

6.7.5.5. Patient Global Impression of Change scale (PGI-C) in Adults

PGI-C will be completed every 14 days. Adult participants enrolled under global CSP amendment 2 and later will complete the PGI-C on an electronic device where validated translations are available in the local language. Participants enrolled prior to global CSP amendment 2 will not complete the PGI-C.

The PGI-C assesses the change of overall status since the start of the study. The response options of the PGI-C are scored using a 7-point scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; 7 = Very Much Worse. Values less than 4 indicate an improvement, while values greater than 4 indicate worsening since start of the study.

No additional scoring will be performed for the PGI-C. If PGI-C was assessed more than once within 2 weeks, the observation closest to the target Study Day will be selected; or the latter observation if 2 observations are equally close to the target Study Day. All data will be listed.

6.7.5.6. EQ-5D-5L

A sample of the EQ-5D-5L questionnaire is provided in Appendix F. The EQ-5D-5L questionnaire will be collected at Study Day 1, at Week 4, Week 16, Week 28, Week 40, Week 52 (EOT) and Week 56 (EOS). In case of assessments out of visit window, windowing will be applied as detailed in Section 6.5.

For calculation of the index score, the US value set will be used for all participants.

Baseline is defined as the most recent assessment on or before study day 1.

6.7.5.7. Quality of Life Questionnaire – Primary Ciliary Dyskinesia (QoL-PCD) for Adolescents

QoL-PCD has been added to ASPEN for adolescent participants in countries where translation is available (English, Spanish, Hebrew).

The QoL-PCD is separated as below:

- QoL-PCD for Adolescents (ages 13 to 17 years) includes 38 items divided into two sections, Section I: Quality of Life, and Section II. School, Work, or Daily Activities.
- QoL-PCD for Children (ages 6 to 12 years; questionnaire will be completed for participants at a year of 12 as inclusion into this study requires a minimum age of 12 years) includes 34 items.
- QoL-PCD for Parents / Caregivers (ages 6 to 12 years; questionnaire will be completed for participants at a year of 12 as inclusion into this study requires a minimum age of 12 years) includes 35 items divided into two sections, Section I: Quality of Life, and Section II. Symptoms.

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).

Scoring will be performed as indicated in Appendix B. The QoL-PCD will be collected at Study Day 1, at Week 4, Week 16, Week 28, Week 40, Week 52 (EOT) and Week 56 (EOS).

Baseline is defined as the most recent assessment on or before study day 1.

6.7.5.8. Health care resource utilization

The derivation of hospitalizations per person-year will be done as described in Section 6.7.1.4. The eCRF "*Doctor visits and ER visits YN*" and the corresponding form "*Doctor visits and ER visits log*" will be used to calculate the number of outpatient and ER visits. The record for "*Healthcare visit type*" will differentiate between outpatient visit ("*Doctor office visit*", "*Urgent care visit*") and an ER visit ("*Emergency room visit*").

6.7.5.9. Bronchiectasis Scoring Technique for Computed Tomography and Airway-Artery

Definitions of CT substudy endpoints will be described in a separate SAP.

6.7.5.10. Completion Rates

Completion rates for PRO instruments will be calculated for each domain by timepoint and treatment group. Completion rates are presented as percentages as given below:

$$Completion\_Rate(\%)_{domain,timepoint} = \frac{\#instrument\_received}{\#instrument\_expected} * 100.$$

6.8. Definitions and Derivations of Pharmacodynamic Parameters

Pharmacodynamic parameters are NE, CatG, and PR3.

Sample collection schedules are listed in Appendix H.

Derived activity parameters

The percentage (%) change from baseline in PD parameters will be calculated as

$$PD_{param1}(\%) = (fold_{change} - 1) * 100$$

While the ratio between post-treatment and baseline results defines the fold change:

$$fold\_change = \frac{post\_treatment\ activity}{pre\_treatment\ activity}.$$

Pre-treatment / Baseline

The pre-treatment result is defined as the arithmetic mean of PD parameter results at screening and baseline.

Change from pre-treatment / Change from baseline

$$Change\ from\ pre\_treatment = post\_treatment - pre\_treatment\ .$$

Maximum reduction

The lowest post-treatment change from baseline result will identify the maximum reduction for the respective participant.

Time to maximum reduction

The time to maximum reduction in days will be calculated by participant and parameter as

$$Time\ to\ maximum\ reduction\ (days) = date\ of\ maximum\ reduction - date\ of\ first\ IP\ administration + 1.$$

6.9. Handling of Missing Data

The handling of missing data and appropriate imputations are described in the following sections and will be performed after all efforts fail to obtain the data.

6.9.1. Missing PRO Administrations and Missing Item Responses

Missing individual item PRO responses will not be imputed.

Domain scores will be calculated as per corresponding PRO manual, the derivations are described within corresponding variable section. In case the domain score is not evaluable, it will be treated as missing and will follow the rules specified for missing data handling described within the corresponding efficacy section.

6.9.2. Missing Start and Stop Dates for Prior and Concomitant Medication

The rules to categorize medications to 'Prior' or 'Concomitant' are described in Section 6.4.8. There is no need to impute missing or partially missing start or stop dates.

Special care will be taken for partially reported dates of antibiotic therapy when identifying ICEs:

Incomplete Start Date

In the case where only the day is missing, the following imputation rules will be applied:

- If the month and year are the same as the year and month of the first IP administration date, then the first IP administration date will be assigned to the missing day;
- If either the year of the partial date is before the year of the first IP administration date or the years of the partial date and the first IP administration date are the same, but the month of partial date is before the month of the first IP administration date, then the last day of the month will be assigned to the missing day;
- If either the year of the partial date is after the year of the first IP administration date or the years of the partial date and the first IP administration date are the same, but the month of partial date is after the month of the first IP administration date, then the first day of the month will be assigned to the missing day;
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

In the case where both day and month are missing, the following imputation rules will be applied:

- If the year is the same as the year of the first IP administration date, then the day and month of the first IP administration date will be assigned to the missing fields;
- If the year is prior to the year of the first IP administration date, then December 31 will be assigned to the missing fields;
- If the year is after the year of the first IP administration date, then January 1 will be assigned to the missing fields.

In the case where day, month and year are missing, the therapy will be considered as ongoing throughout participant's study participation.

Incomplete Stop Date

In the case where only the day is missing, the following imputation rules will be applied:

- If the month and year of the incomplete stop date are the same as the month and year of the last IP administration date, then the day of the last IP administration date will be assigned to the missing day;
- If either the year of the partial date is not equal to the year of the last IP administration date or the years of the partial date and the last IP administration date are the same, but the month of partial date is not equal to the month of the last IP administration date, then the last day of the month will be assigned to the missing day.

In the case where both day and month are missing, the following imputation rules will be applied:

- If the year of the incomplete stop date is the same as the year of the last IP administration date, then the day and month of the last IP administration date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last IP administration date or prior to the year of the randomization date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last IP administration date but is the same as the year of the randomization date, then the randomization date will be assigned to the missing date.
- If the year of the incomplete stop date is after the year of the last IP administration date, then January 1 will be assigned to the missing fields.

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

6.9.3. Missing Start and Stop Dates for Adverse Events

The rules to categorize AEs to 'TEAE' or 'non-TEAE' are described in Section 9.2. There is no need to impute missing or partially missing start or stop dates.

6.9.4. Missing Dates for Time since Diagnosis

The following rules will be applied for partial dates of bronchiectasis diagnosis:

- if only the day is missing, the first day of the month will be assumed;
- if the day and the month are missing, January 1st will be assumed.

7. STUDY POPULATION SUMMARIES

Data will be displayed separately by treatment groups and total (see Section 6.4.2) unless otherwise stated.

7.1. Participant Disposition

The participant disposition will be based on the Screened Analysis Set (see Section 5.1).

For participants screened, the number of participants who are screened, the number and percent of participants who continue into the study, and the number of participants who failed screening, the reasons for screen failure, and relationship of screen failure to COVID-19 will be summarized. In addition, the participant disposition will include the number and percentage of participants who are:

- randomized,
- excluded from analysis due to war in Ukraine,
- excluded from analysis due to serious GCP noncompliance (site USA065),
- did not receive IP,
- completed/discontinued from the study or IP and the reason for discontinuation (including relation to COVID-19),
- ongoing study or IP at primary database lock.

Number of participants included in each of the analysis sets will be summarized as counts and percentages, too.

7.2. Protocol Deviations

Deviations from the study protocol will be monitored throughout the conduct of the study.

Major protocol deviations that may affect the primary efficacy and/or safety assessments (as applicable), the safety or mental integrity of a participant, or the scientific value of the study will be summarized descriptively. Tabulations will be based on the ITT Analysis Set (see Section 5.2).

7.3. Demographic and Baseline Characteristics

Demographic and baseline characteristic variables will be summarized for all Analysis Sets as defined in Section 5. A summary by region will be provided, too. The summary will include:

- country,
- age,
- age group (12 to <18years, 18 to <65 years, >= 65 years),
- age group >=18 years,
- age group (<75 years, >=75 years),
- sex,
- ethnicity,
- race,
- Baseline height,
- Baseline BMI,
- Baseline FEV1, pre- and post-bronchodilator (in L and % Predicted),
- Baseline FEV1 (% Predicted) < 50%,
- History of Chronic Obstructive Pulmonary Disease, identified through MedDRA coded terms (see Appendix K),
- History of Asthma, identified through MedDRA coded terms (see Appendix K),
- Hospitalized in prior 24 months for PE,
- CT Scan confirmation of Bronchiectasis,
- Use of Inhaled Steroids, identified through ATC coded terms (see Appendix K),
- Chronic use of Antibiotics,
- Bronchiectasis Severity Index (BSI) (see Appendix L),
- BSI categories (<=4, 5-8, >=9),
- Smoking status, including pack-years smoked (refer to Section 6.4.6 for calculation of pack-years smoked),
- Baseline eosinophil count (>=300/mm3, <300/mm3),
- Baseline QoL-B Respiratory Symptoms Domain Score (adults),
- Baseline BE-CT Score
- the stratification variables region (North America, Europe, Japan, and Rest of World), sputum sample (positive or negative for *Pseudomonas aeruginosa*) and the number of PEs in the previous 12 months (<3, >=3). Stratification variables will be presented as used for randomization.
- Geographic Region (South America, Eastern Europe, Western Countries, Asian Countries)

The distribution of participants randomized across region, country, and site will be presented for the ITT analysis set.

In addition, a listing will be produced for mismatches between randomized and actual strata.

7.3.1. Medical History and Indication History of NCFBE

All medical history records will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized for the ITT and Safety Analysis Set using counts and percentages by System Organ Class (SOC) and Preferred Term (PT). Participants are counted only once in each SOC and only once in each PT.

Indication history will summarize the time since bronchiectasis diagnosis, etiology, PEs reported in the past 12 months before screening, and whether antibiotic prescription was documented.

The time since diagnosis will be calculated as below. For handling partial dates, refer to Section 6.9.4.

$$time\ since\ diagnosis\ (days) = date\ of\ randomization - date\ of\ bronchiectasis\ diagnosis - + 1.$$

7.4. COVID-19 Impact

Potential COVID-19 impact is captured in the eCRF and will be summarized by participant.

Participant disposition summary and listing will include (see Section 7.1):

- Screen failure related to COVID-19,
- Treatment discontinuation related to COVID-19,
- Early termination of study related to COVID-19.

AE overview table and listings will include (see Section 9.2):

- COVID-19 AEs.
- In addition, correlation between COVID-19 AEs within +/-30 days of an exacerbation event that meet the protocol definition of PE diagnosis based on independent adjudication process start and end date will be investigated (see Section 9.2).
- COVID-19 AEs by region and time period:
    - Start of study to 30-Jun-2021
    - 01-Jul-2021 to 15-Dec-2021
    - since 16-Dec-2021

Summary table and listing of missed IP / IP discontinuation will include (see Section 9.1):

- Missed IP due to COVID-19.
- IP discontinuation due to COVID-19.

Summary and listing of protocol deviations will include (see Section 7.2):

- Protocol deviations due to COVID-19.

8. EFFICACY

8.1. Hypotheses

There are 3 possible pairwise comparisons among the treatment arms for the efficacy endpoints. Only treatment versus placebo comparisons will be shown. The two comparisons are of principal interest and will be conducted for superiority: brensocatib 10 mg vs placebo and brensocatib 25 mg vs placebo. The corresponding null ($H_{0.}$) and alternative ($H_{1.}$) hypotheses for the primary endpoint are:

1. $H_{01}: \frac{\lambda_{10\,mg}}{\lambda_{Placebo}} = 1$ vs $H_{11}: \frac{\lambda_{10\,mg}}{\lambda_{Placebo}} \neq 1$
2. $H_{02}: \frac{\lambda_{25\,mg}}{\lambda_{Placebo}} = 1$ vs $H_{12}: \frac{\lambda_{25\,mg}}{\lambda_{Placebo}} \neq 1$

where λ represents the mean rate of pulmonary exacerbations. The null ($H_{0.}$) and alternative ($H_{1.}$) hypotheses for testing of the secondary endpoints are defined similarly. All superiority comparisons will be two-sided with test-specific alpha as per the multiple testing procedure described in Section 6.3.

8.2. Primary Endpoint – Annualized Rate of Pulmonary Exacerbations

The primary efficacy endpoint is the Annualized Rate of PEs (including severe PEs) that have been confirmed through the event adjudication process (see Section 6.7.1).

8.2.1. Main Analyses

The Primary Estimand is the On-Study Estimand in which all observed data up to Week 52 will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used for this Estimand.

The Annualized Rate of PEs will be analyzed using negative binomial regression as implemented in SAS® PROC GENMOD with robust estimate for the covariance matrix. The latter will be achieved by introducing a REPEATED-Statement identifying participant-ID with TYPE=UNSTR[4] for the covariance as unstructured. The model will include treatment group and the randomization stratification factors (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, stratification region [North America, Europe, Japan, and the Rest of the World]), and age group (adult, adolescent) as fixed effects. If the age group covariate creates estimability issues, it may be removed. If the model still does not converge after removing the age group covariate, other handling including using the parametric covariance estimator instead of the robust sandwich covariance estimator may be applied. The time at risk in years (log scale) will be included in the model as an offset variable. The LOG-link function will be used in the model. The OM option will be used to adjust the co-

[4] TYPE=UNSTR option specifies that the covariance matrix of the scores be estimated empirically.

efficients for the LSMEANS to reflect the observed data. An example SAS code can be found in Appendix I.

The annualized Rate of PE 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. In addition, the frequency distribution of participants experiencing 0, 1, 2, 3, and >=4 exacerbations will be provided.

Occurrence of exacerbation events that meet the protocol definition of PE diagnosis based on independent adjudication process will be explored graphically. The below histograms will be produced. Treatment groups will be distinguished by separate bars.

- Count of PEs reported every month in study starting at Day 1 through Week 52. Differentiation of PEs into study month is detailed in Section 6.7.1.7.
- Mean Cumulative Function of PEs reported starting at Day 1 through Week 52 will be created (see Appendix I for technical details)
- Count of PEs within the categories: “0”, “1”, “2”, and “>=3”

8.2.2. Sensitivity Analyses – Tipping Point

If there are study participants who discontinue randomized IP early and decline to remain in the study, ascertainment of data will be incomplete, and a true Treatment Policy/ITT analysis cannot be achieved. A “missing at random” (MAR) assumption for the missing data is made implicitly for the On-Study Estimand.

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, i.e., missing not at random (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.

As the first step, multiple imputations (MI) of missing PE data under the observed data model (MAR assumption) will be implemented using negative binomial model, which models the distribution of a response Y, e.g., the number of PE events, as the joint distribution of the observed responses Y_{obs} and a distribution of the missing responses Y_{mis} after discontinuation from the study. Missing post withdrawal PEs will be imputed with the predicted PE values from the model, per treatment and strata, for the time remaining after study discontinuation prior to Week 52. Refer to Figure 2 as a visualization of the different periods of a participant’s participation who discontinued early from study.

Figure 2: Sensitivity Analysis: Period of Discontinued Participants

For a given participant, the conditional distribution $Y_{mis}|Y_{obs}$ is a function of the observed events y_1, the estimated dispersion, the estimated PE rate in period 1 (which is the same as obtained in the primary analysis) and the model covariates. The imputed count of PEs will be combined with the observed PE count. The process of imputing missing PE data will be repeated multiple times to create 100 separate datasets.

As the second step, a penalty (delta) will be applied to the imputed data prior to analyzing each of the separate data sets. For each brensocatib dose comparison relative to placebo, the tipping point penalties (delta adjustment) will be applied in a bi-directional manner. That is, the PE rate (after imputation) for the MNAR data in the brensocatib arms will be incrementally increased, while the PE rate for the MNAR data in the placebo arm will be incrementally decreased. With each increment, the 100 complete data sets will each be analyzed using the same model as for the primary analysis. The analysis results for each increment will be combined using Rubin's rules (Rubin 1987).

This process of incrementing the penalties will continue until the respective comparison is no longer statistically significant at two-sided α= 0.01 (i.e., the Tipping Point) per the multiple testing procedure described in Section 6.3 or until the PE rate has been incremented until 3-fold the observed reduction has been achieved.

The delta penalties to be investigated are pre-selected multiples of the observed rate reduction. If the observed rate ratio reduction from the primary analysis is x, the deltas to be investigated will range from 1-x to 1+3*x for both active and the placebo arms, in increments of 0.5*x (for example, if the observed rate reduction is 30% [x=0.3] the imputed rates will be multiplied by deltas of 0.7 to 1.9 in increments of 0.15) as shown in Table 7. The increment or range may be refined based on analysis results and the location of tipping point.

The grid below provides an example of the bi-directional delta increment/decrement for the comparison of brensocatib 25 mg vs placebo. Note, some of the intermediary cells (delta increments) have been eliminated for brevity. The post-withdrawal mean rate is calculated as the delta*mean rate under the MAR assumption (where z=mean rate under MAR assumption for brensocatib 25 mg; y=mean rate under MAR assumption for placebo). The cell with delta = 1 for both brensocatib 25 mg and placebo represents the primary analysis result under MAR (see Section 8.2.1).

Table 7: Primary Endpoint: Tipping Point Analysis –Delta Increment / Decrement

			Brensocatib 25 mg				
			Delta				
			0.70	1.00	1.30	1.60	1.90
Placebo	**Delta**	**Mean Rate Post Withdrawal**	(1-x)*z	1*z	(1+x)*z	(1+2*x)*z	(1+3*x)*z
	1.90	(1+3*x)*y					
	1.60	(1+2*x)*y					
	1.30	(1+x)*y					
	1.00	1*y					
	0.70	(1-x)*y					

Some of the intermediate steps left out for brevity.

For each of the above cells, complete sets of exacerbation data (observed and imputed) for the 3 treatment arms will be generated using multiple imputation under the MAR assumption. The imputation model will contain the same covariates as in the primary analysis model (Section 8.2.1). Missing data are assumed to be MNAR and will then have the corresponding delta applied. One hundred (100) separate complete data sets for each of the relevant cells will be generated and analyzed. The log-scale results will be combined using Rubin's method (Rubin 1987) and then exponentiated to obtain final estimates for the rates and rate ratios. The relevant delta increment/decrement grid for each brensocatib dose comparison will be populated with the corresponding p-values. Should a Tipping Point be identified, the plausibility of the assumptions surrounding the MNAR data (i.e., magnitude of the delta adjustments in both treatment arms) will be assessed from a clinical perspective.

Technical details for the implementation in SAS can be found in Appendix I.

8.2.3. Supplementary Analyses – Time at Risk Replaced by the Total Time on Study

A supplementary analysis will be performed by repeating the primary analysis and re-defining participants time at risk. Time at risk will be the participants total time on study:

- Date of EOT – date of randomization + 1: for participants completing 52 weeks of treatment period;
- For participants who discontinue from treatment and study at the same time: Date of EOS/discontinuation – date of randomization + 1.
  For participants who discontinue from treatment but remain in the study, the minimum duration between date of randomization and the (theoretical) date of Week 52:
  364 (day) or
  the date of EOS/discontinuation – date of randomization + 1
  will be used for the On-Study Estimand.

The duration of PEs will be ignored in this analysis.

8.2.4. Sensitivity Analyses – Reference-Based-Multiple-Imputation

A Jump-to-Reference sensitivity analysis will be performed where the Placebo arm will act as the reference arm. All data with an assessment or visit date prior to the time of the first of any ICE (see Section 2) will be included. Data with an assessment or visit date after occurrence of an ICE related to treatment failure (e.g., early discontinuation from randomized treatment for lack of efficacy, treatment discontinuation due to AE, or start of additional chronic antibiotics) will be considered missing and imputed.

Multiple imputations will be used to replace missing outcomes for brensocatib- and placebo-treated study participants.

To note, the need for this sensitivity analysis will be evaluated during the BDRM prior to database lock and unblinding of the study. It will be conducted and included in the CSR if there are a non-trivial number of ICEs related to treatment failure.

8.2.5. Supplementary Analyses

The supplementary Estimands for the primary endpoint are the On-IP and the On-Treatment Estimands (see Section 2) and will utilize the ITT Analysis Set (see Section 5.2). The same negative binomial regression model as applied for the main analysis will be implemented for this Estimand (see Section 8.2.1). The analysis will be repeated by including all exacerbations designated "Clinically Relevant" by the adjudication committee per Section 11.3 of the CEC Charter. The same model will be used as for the primary analysis including the combining of PEs as discussed in Section 6.7.1.1.

8.2.6. Subgroup Analyses

Consistency of observed treatment effect on the Annualized Rate of PEs will be explored across major subgroups as shown in the list below.

- Age (12- <18, 18-<65 years, ≥65 years); (<75 years, ≥75 years); (>=18 years),
- Sex (Male, Female),
- All race groups (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- Number of PEs in prior 12 months (<3, ≥3),
- Chronic use of Antibiotics at Baseline (Yes, No),
- Maintenance use of macrolides at Baseline (Yes, No),
- *Pseudomonas aeruginosa* colonization at Baseline (Positive, Negative),
- (Re-calculated) BSI score (≤4, 5-8, ≥9),
- Baseline BSI score (< Median, ≥ Median),
- BE-CT score (< Median, ≥ Median),
- Baseline FEV1 % Predicted (<50%, ≥50%) post-bronchodilator,
- Stratification region (North America, Europe, Japan, the Rest of World),
- Geographical region (South America, Eastern Europe, Western Countries, Asian Countries, Oceania)
- Baseline eosinophil count (>=300/mm3, <300/mm3),
- Smoking status (Former smoker, Never smoked,),
- Use of inhaled steroids (Yes, No),
- History of Asthma, identified through MedDRA coded terms (see Appendix K) (Yes, No),
- History of Chronic Obstructive Pulmonary Disease, identified through MedDRA coded terms (see Appendix K) (Yes, No),

- Hospitalized in prior 24 months for PE (Yes, No).

Subgroup analysis will be based on a similar negative binomial model as used for the primary analysis (see Section 8.2.1). The covariate of age group will not be included in models for subgroup analyses. One model per subgroup parameter will be fitted, omitting the fixed effect if it's identical to the subgroup or confounded with the subgroup. Crosstabulation of subgroup levels versus covariate levels via PROC FREQ will be utilized to identify any confounding. The ITT Analysis Set (see Section 5.2) 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 with annualized rate ratio of PEs and 95% CI will be displayed for each level of all subgroup parameters.

For adolescent subgroup (Age 12-<18), a Bayesian approach that borrows information from the adult subgroup (Age >= 18) will be explored to inform efficacy on the primary endpoint. The prior distribution of the Bayesian approach will be a mixture of a non-informative prior and a distribution of the treatment effects in adults, with the mixing weight ranging from 0 (no borrowing) to 1 (full borrowing) in increments of 0.05 to allow a complete view of the spectrum of outcome The analysis will be performed for each dose separately. The posterior mean and 95% credible intervals will be calculated for each weight value and presented in a figure.

The analysis for the annualized rate of PEs in the adult subgroup (Age >= 18) will also be conducted for the On Treatment Estimand.

8.3. Secondary Endpoints

8.3.1. Time to First Pulmonary Exacerbation

8.3.1.1. Main Analyses

The Main Estimand of the time to first PE is the On-Study Estimand in which all observed data will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used for this Estimand. The derivation of the endpoint is detailed in Section 6.7.1.6.

Cumulative first PE incidence rates over the 52-Week treatment period will be calculated using the Kaplan-Meier method. The summary will include the number of participants with at least 1 PE and the number of participants without any events (censored). A covariate-adjusted Cox proportional hazards regression model including fixed effects for treatment group, 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, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) will be fitted using the PHREG procedure with the robust sandwich estimate for the covariance matrix in SAS (option COVSANDWICH(AGGREGATE) in the procedure-statement). If the age group covariate creates estimability issues, it may be removed. If the model still does not converge after removing the age group covariate, other handling including using the parametric covariance estimator instead of the robust sandwich covariance estimator may be applied. The CLASS statement will identify covariates while the model will be identified in the MODEL statement. Results will be summarized in a table including number and percentage of participants with PEs, estimated hazard ratio and 95%

confidence limits. The 2-sided Wald p-value from the Cox model will be compared to the appropriate alpha level per the multiple test procedure. Technical details for the implementation in SAS can be found in Appendix I.

Kaplan-Meier estimates of the median including 95% confidence interval will be presented.

The effect over time will be illustrated with a plot of the complement (1 – Kaplan-Meier estimates).

8.3.1.2. Sensitivity Analyses

The analysis of time to first PE over the 52-Week treatment period is planned to be performed under the assumption that observations that are censored prior to Week 52 are censored-at-random (CAR) and that censoring is uninformative; meaning that censoring times and event times are independent. There is no plan to impute missing event times in the main analysis.

A tipping point analysis will be used as a sensitivity analysis to examine the effect of potential departures from the CAR assumption, e.g., censored-not-at-random (CNAR), in the main analysis. Due to the inherent difficulties in identifying the missing data mechanism in practice, all missing data (i.e., censoring prior to Week 52) will be assumed CNAR, and the tipping point penalties will be applied accordingly.

As the first step, an additional penalty (delta) will be applied to the assumed hazard rates for the CNAR data. For each brensocatib dose comparison relative to placebo, the tipping point penalties (delta adjustment) will be applied in a bi-directional manner. That is, the hazard rate for the CNAR data in the brensocatib arms will be incrementally increased. This worsening outlook is quantified by a sensitivity parameter δ interpreted as an increased hazard of PE event post-dropout, while the hazard rate for the CNAR data in the placebo arm will be incrementally decreased. This process of incrementing the penalties will continue until the respective comparison is no longer statistically significant (i.e., the Tipping Point) per the multiple testing procedure described in Section 6.3 or until the unlikely incremented/decremented hazard rate has been achieved.

As the second step, MI of the missing first PE event times under the hazard rate assumptions will be implemented using Cox model. Post study withdrawal first PE event times will be imputed conditional upon hazard rate assumptions. The process of imputing the first PE missing event times will be repeated multiple times to create 100 separate data sets. If the imputed first event times are greater than 52 weeks, the participants will be censored at Week 52.

With each increment, the 100 complete data sets will each be analyzed using the same model as for the main analysis. The analysis results for each increment will be combined using Rubin's rules (Rubin 1987).

The relevant delta increment/decrement grid for each brensocatib dose comparison will be populated with the corresponding p-values. Should a Tipping Point be identified, the plausibility of the assumptions surrounding the CNAR data (i.e., magnitude of the delta adjustments in both treatment arms) will be assessed from a clinical perspective.

Hazard ratios and 95% Cis for the hazard ratio corresponding to each value of δ will be presented in a similar manner as described under the main analysis.

Technical details for the implementation in SAS can be found in Appendix I.

8.3.1.3. Supplementary Analyses

The supplementary Estimand for the time to first PE over the 52-Week treatment period is the On-IP Estimand (see Section 2) and will utilize the ITT Analysis Set (see Section 5.2). The time-to-event model of the main analysis will be implemented for this Estimand (see Section 8.3.1.1). Participants who do not have an event during the 52-Week treatment period will be censored at the day of last treatment administration.

8.3.2. Responder Status for Exacerbation-Free over the 52-Week Treatment Period

8.3.2.1. Main Analyses

The Estimand of the responder status for exacerbation-free over the 52-week treatment period is the On-Study Estimand in which all observed data will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used for this Estimand. The derivation of the endpoint is detailed in Section 6.7.2.

The number and percentage of Responders/Non-responders over the 52-Week Treatment Period will be presented by treatment group.

Responder status at Week 52 will be compared between treatment groups brensocatib vs. placebo using a logistic regression model including treatment group, 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, stratification region (North America, Europe, Japan, and the Rest of the World) , and age group (adult, adolescent) as fixed effects. If the age group covariate creates estimability issues, it may be removed. An estimate of the odds ratio for the treatment comparison (brensocatib 10mg vs. placebo; brensocatib 25mg vs. placebo) and the 95% Wald confidence interval will be summarized; the corresponding p-value from the Wald chi-square test will be compared to the appropriate alpha level per the multiple test procedure.

For participants who discontinue the study prior to Week 52 without having experienced a PE confirmed through adjudication, their responder status will be missing. To address this issue, first event times for these participants will be imputed based on the observed data model for the time period after discontinuation from the trial. If the imputed event time occurs prior to Week 52, the participant will be considered a non-responder. Otherwise, the participant will be considered a responder. The process of imputing missing PE data will be repeated multiple times to create 100 separate datasets. With each increment, the 100 complete data sets will each be analyzed using the logistic regression model described above. The analysis results will then be combined using Rubin's rules (Rubin 1987).

Technical details for the implementation in SAS can be found in Appendix I.

8.3.2.2. Sensitivity / Supplementary Analyses

The supplementary Estimand for the responder status for exacerbation-free over the 52-week treatment period is the Composite Estimand (see Section 2) and will utilize the ITT Analysis Set (see Section 5.2). The derivation of the endpoint is detailed in Section 6.7.2. A similar logistic regression model as for the On-Study Estimand will be used for the responder status data of the Composite Estimand.

8.3.3. Change from Baseline in Post-bronchodilator FEV1 (L) at Week 52

8.3.3.1. Main Analyses

The Main Estimand of the change from baseline in post-bronchodilator FEV_1 (L) at Week 52 is the On-Study Estimand in which all observed data will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used for this Estimand. The derivation of the endpoint is detailed in Section 6.7.3. Tabulations described below will not be limited to Week 52 but summarize all scheduled time points.

Pre- and post-bronchodilator FEV_1 assessments at baseline and Weeks 16, 28, 40, 52 will be summarized by treatment group using descriptive statistics. The summary will include changes from baseline, too.

Change from baseline in post-bronchodilator FEV_1 (L) will be analyzed using a linear repeated measures model including treatment group, visit, treatment-by-visit interaction, 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, stratification region (North America, Europe, Japan, and the Rest of the World), and age group (adult, adolescent) as fixed effects, and baseline value as covariate. The variance-covariance structure will be compound symmetric with the robust sandwich variance estimator (option EMPIRICAL in the PROC-Statement). This analysis will be performed in SAS using MIXED procedure. The OM option will be used to adjust the coefficients for the LSMEANS to reflect the observed data.

If the age group covariate creates estimability issues, it may be removed. If the model still does not converge after removing the age group covariate, other handling including using the parametric covariance estimator instead of the robust sandwich covariance estimator may be applied. When using the parametric covariance estimator, the restricted maximum likelihood (REML) estimator will be applied, with the variance-covariance structure being applied with the following sequence: UN -> TOEPH -> ARH(1) -> CSH. If the model still does not converge, the maximum likelihood estimator will be applied instead of the REML estimator, with the same sequence of the possible variance-covariance structures. The adjustment will be added to the footnote of the corresponding outputs.

The adjusted means in each treatment group, the adjusted mean differences between treatments, and their 95% Cis at Week 52 will be presented. The p-value for the adjusted mean difference will be compared to the appropriate alpha level per the multiple test procedure.

A figure displaying the adjusted mean changes from baseline over time by treatment group will be provided.

8.3.3.2. Sensitivity Analyses

A tipping point analysis will be used to investigate the impact of missing data and to examine the robustness of the main analysis. The tipping point will be identified when the respective comparison is no longer statistically significant at two-sided $\alpha = 0.05$.

To explore the impact of missing data on the mean treatment effect, different assumptions of the effect will be evaluated by adding an additional penalty (delta) prior to analyzing the imputed datasets and combining the results. For each brensocatib dose comparison relative to placebo, the tipping point penalties (delta adjustment) will be applied in a bi-directional manner. The deltas or delta adjustments are pre-selected multiples of the observed treatment effect. If the observed mean treatment effect from the main analysis is x, the deltas to be investigated will range from -3*x to 0 for the active arm, in increments of 10 mL. The delta adjustments to be applied to the imputed data in placebo arm will range from 0 to 3*x. The increment or range may be refined based on the analysis results and the location of the tipping point.

All recorded data up to and including the Week 52 assessment (see Section 2) will be included. Missing data will be imputed using multiple imputation first based on the MAR mechanism. The imputation model will contain the same covariates as in the main analysis model (see Section 8.3.3.1). 100 separate complete data sets for each comparison within the pre-selected delta range will be generated and analyzed. Markov Chain Monte Carlo (MCMC) method will be used to fill intermittent missing values, e.g., missing values between reported visits, under the assumption of MAR, resulting in an intermediate data with monotone missing patterns. MCMC will use a separate chain for each imputation (multiple chains), a non-informative prior for the means and covariances, and 200 burn-in iterations before the very first imputation in each chain. For monotone missing data the regression method will be applied using a separate regression for each of the non-monotone imputed datasets. Results will be combined across imputations using Rubin's method (Rubin 1987). The relevant delta decrement grid for each brensocatib dose vs. placebo comparison will be populated with the corresponding p-value.

Technical details for the implementation in SAS can be found in Appendix I.

8.3.3.3. Supplementary Analyses

The supplementary Estimand for the change from baseline in post-bronchodilator FEV_1 (L) at Week 52 is the On-IP Estimand (see Section 2) and will utilize the ITT Analysis Set (see Section 5.2). The same model as used for the main analysis will be implemented for this Estimand (see Section 8.3.3.1).

8.3.4. Annualized Rate of Severe Pulmonary Exacerbations

8.3.4.1. Main Analyses

The Estimand of the Annualized Rate of Severe PEs is the On-Study Estimand in which all observed data will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used for this Estimand. The derivation of the endpoint is detailed in Section 6.7.4.

The analytical approach as outlined for the primary endpoint in Section 8.2.1 will be applied to the Annualized Rate of Severe PEs. The rate ratios for comparison between treatments and their 95% Cis will be presented along with the corresponding Wald p-value.

8.3.4.2. Sensitivity Analyses

The analytical approach of the sensitivity analysis described in Section 8.2.2 will be applied for severe PEs with the difference, that death from any cause will be counted as a severe PE.

8.3.4.3. Supplementary Analyses

The supplementary Estimand for the Annualized Rate of Severe PEs is the On-IP Estimand (see Section 2) and will utilize the ITT Analysis Set (see Section 5.2). The same negative binomial regression model as applied for the primary analysis will be implemented for this Estimand (see Section 8.2.1).

8.3.5. Change from Baseline in QoL-B Respiratory Symptoms Domain Score at Week 52

The QoL-B is a validated, self-administered, patient reported outcome questionnaire used to assess symptoms, functioning, and health related quality of life in adults with non-CF bronchiectasis (Quittner, 2015). It measures outcomes over a recall period of 1 week. The questionnaire contains 37 items on 8 scales (physical, role, vitality, emotional, social, treatment burden, health perception, and respiratory).

There is no total score for QoL-B. Calculation of scale (domain) scores is described in Appendix A.

8.3.5.1. Main Analyses

The Main Estimand of the change from baseline in QoL-B Respiratory Symptoms Domain Score at Week 52 is the On-Study Estimand in which all observed data will be included in the analysis (see Section 2). The population attribute for this Estimand is adult participants with NCFBE who meet all inclusion criteria and none of the exclusion criteria. The ITT Analysis Set (see Section 5.2) will be used for this Estimand.

Calculated Respiratory Symptoms score (items 29 to 37) will be summarized at baseline and change from baseline at Week 52 by treatment group using descriptive statistics. Single item responses (each question) will be summarized by treatment group in a shift table. Completion rates will be presented by time point (see Section 6.7.5.10).

Change from baseline of calculated Respiratory Symptoms score (items 29 to 37) at Week 52 will be analyzed using a linear repeated measures model including treatment group, visit, treatment-by-visit interaction, sputum sample being classified as positive or negative for *Pseudomonas aeruginosa* at Screening Visit, the number of prior PEs [<3, ≥3] in the previous 12 months and stratification region (North America, Europe, Japan, and the Rest of the World) as fixed effects, and baseline value as covariate. Given that the QoL-B will be administered every two weeks for a total of 26 time points, estimation of a complex variance-covariance structure with many parameters will be untenable. Therefore, the variance-covariance structure will be compound symmetric with the robust sandwich variance

estimator. Results will be presented in the same manner as the analysis of "*Change from Baseline in Post-bronchodilator FEV1 (L) at Week 52*" (see Section 8.3.3), including a figure displaying the adjusted means and corresponding 95% confidence intervals at Week 52 by treatment group. The OM option will be used to adjust the co-efficients for the LSMEANS to reflect the observed data. The between-treatment differences and corresponding 95% CIs will be presented; the associated p-value for the adjusted mean difference will be compared to the appropriate alpha level per the multiple test procedure.

If the model fails to achieve convergence, similar handling described in Section 8.3.1.1 Main analysis for Change from Baseline in Post-bronchodilator FEV_1 (L) at Week 52 will be applied and the adjustment will be added to the footnote of the corresponding outputs.

8.3.5.2. Sensitivity Analyses

The analytical approach of the sensitivity analysis described in Section 8.3.3.2 will be applied for the change from baseline in QoL-B Respiratory Symptoms Domain Score at Week 52.

8.3.5.3. Supplementary Analyses

The supplementary Estimand for the change from baseline in QoL-B Respiratory Symptoms Domain Score at Week 52 is the On-IP Estimand (see Section 2) and will utilize the ITT Analysis Set (see Section 5.2). Technical details for the implementation in SAS can be found in Appendix I.

The same linear model as used for the main analysis will be implemented for this Estimand (see Section 8.3.5.1).

As there is no universally accepted meaningful change threshold that can be prespecified for responder analyses of the Qol-B Respiratory Symptoms domain score, cumulative responder curves (Farrar et al. 2006) will be generated for the On-IP Estimand. Change from baseline at Week 52 will be plotted on the x-axis, and the proportion of responders (i.e., participants that equal or exceed that level of change) on the y-axis. A separate curve will be produced for each treatment on the same graph. Participants with missing data will be considered non-responders. Pairwise comparisons of the cumulative responder curves will be conducted using the Kolmogorov-Smirnov test.

8.3.5.4. Identification of the Meaningful Change Threshold

The meaningful change threshold (MCT) will be estimated from the ASPEN data by applying an anchor-based approach using the PGI-S and PGI-C assessments as anchors at Week 52. The MCT will be supplemented with distribution-based analyses, empirical cumulative distribution function (eCDF) curves, and probability density function (ePDF) curves to provide supportive information. All treatment groups will be pooled. The MCT evaluation will be addressed in a separate document.

Responder status for Change from Baseline in QoL-B Respiratory Symptoms Domain Score at Week 52 will be determined utilizing the identified MCT. Participants with QoL-B Respiratory Symptoms Domain Score missing at Week 52 and available at Baseline will be considered as non-responders, while participants with QoL-B Respiratory Symptoms Domain Score missing at Baseline will be excluded from the analysis. Statistical analysis for the

responder status will be similar to the main analysis approach for the secondary endpoint of Responder Status for exacerbation-free over the 52-week treatment period.

8.3.6. Subgroup Analyses

Subgroup analyses for all secondary endpoints will be reported for the On-Study Estimand based on the groupings defined in Section 8.2.6. However, analyses of QoL-B which is applicable for adults only, will exclude the adolescent subgroup. In addition, the main analysis for 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.

Subgroup analysis will be displayed in tabulations and forest plots.

8.4. Intercurrent Event Assessment

The frequency and percentage of participants experiencing each of the ICE types (see Section 6.2.1) will be tabulated by treatment group. The ICE of addition of a new chronic antibiotic will be further broken down by its subtypes, if applicable. In addition, the time to first ICE will be analyzed in a manner like the analysis of time to first PE, including a plot of the complement (1 – Kaplan-Meier estimates) (see Section 8.3.1.1).

8.5. Exploratory Endpoints

In participants with NCFBE, the exploratory objectives are as described in protocol section 2.3.

Table 8: Exploratory Endpoints

Variable	Population Level Summary	Estimand Name	Treatment Regimen	ICEs/ Strategy	Section
Average Daily Change from Baseline in Bronchiectasis Exacerbation and Symptom Tool (BEST) score Over the 52-Week Treatment Period	Mean Difference	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.5.1
Duration of exacerbation events that meet the protocol definition of PE diagnosis Over the 52-Week Treatment Period	Mean Difference	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.5.2
Days Hospitalized for Adjudicated PEs per patient year Over the 52-Week Treatment Period	Mean Annualized Rate	On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment	8.5.3
Days of Absence from Work/School Related to Adjudicated PEs per Patient Year Over the 52-Week Treatment Period	Mean Annualized Rate	On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment	8.5.4

Change from Baseline in prebronchodilator and postbronchodilator FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), percent predicted forced expiratory flow in 1 second ($ppFEV_1$) and forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{[25-75\%]}$) at Weeks 16, 28, 40, and 52	Mean Difference	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.5.5
Outpatient Visits, emergency room (ER) visits, and hospitalizations for any reason	Mean Annualized Rate	On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment	8.5.6
Change in QOL-PCD Domain Scores From Baseline to Weeks 16, 28, 40, and 52 in Adolescent Participants (≥12 to <18 Years of age) with PCD	Mean Difference	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP / Treatment Policy Modification to standard of care / Treatment Policy	8.5.10
Change from Baseline in EuroQoL-5 Dimension-5 Level Questionnaire (EQ-5D-5L) score to Week 52	Mean absolute value and mean change from baseline	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP /Treatment Policy Modification to standard of care/ Treatment Policy	8.5.8

Change from Baseline in QoL-B Domain Scores to Weeks 16, 28, 40, and 52 in Adult participants	Mean Difference	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP /Treatment Policy Modification to standard of care/ Treatment Policy	8.5.9
PGI-C and the Change from Baseline in PGI-S at Weeks 16, 28, 40, and 52 in Adult participants	Mean Difference	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP /Treatment Policy Modification to standard of care/ Treatment Policy	8.5.10
Rate of Change in Prebronchodilator and Postbronchodilator FEV1 Over the 52-Week Treatment Period	Slope	On-Study	Assignment to IP regardless of discontinuation or modifications to standard of care	Early discontinuation from randomized IP /Treatment Policy Modification to standard of care/ Treatment Policy	8.5.11
Change from Baseline in Bronchiectasis Scoring Technique for Computed Tomography (BEST-CT) and Airway-Artery (AA) Scores at Week 52	Mean absolute value and mean change from baseline	On-Treatment	Standard of care + randomized IP	Early discontinuation from randomized IP / While On-Treatment Early discontinuation from standard of care/ While On-Treatment	8.5.12
Change from Baseline in Concentration of biomarkers (Neutrophil Elastase [NE],	Mean Difference	On-IP	Randomized IP regardless of	Early discontinuation from randomized IP / While On-Treatment	11.1

Cathepsin G [CatG], Proteinase 3 [PR3]) in Sputum to Week 52			modifications to standard of care		
Change from Baseline in Concentration of biomarkers (NE, CatG, PR3, and neutrophil functions) in Blood to Week 52	Mean Difference	On-IP	Randomized IP regardless of modifications to standard of care	Early discontinuation from randomized IP / While On-Treatment	11.2

8.5.1. Average Daily Change from Baseline in BEST Score Over the 52-Week Treatment Period

The Estimand of the average BEST Score is the On-Study Estimand in which all observed data will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used for this Estimand. The derivation of the endpoint is detailed in Section 6.7.5.3.

The average daily change from baseline in the BEST score over the 52-week treatment period will be analyzed with an analysis of covariance model. The model will contain main effects[5] for treatment group, 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 stratification region (North America, Europe, Japan, and the Rest of the World). The baseline BEST score will be included as a covariate. The OM option will be used to adjust the co-efficients for the LSMEANS to reflect the observed data. The adjusted means in each treatment group, the adjusted mean differences between treatments, their 95% CIs and associated p-values will be presented. Completion rates at baseline and at Week 52 will be presented (see Section 6.7.5.10).

Mean BEST score changes from baseline over time will be plotted by study day to assess trends over time. The time axis will be limited to 365 days. No tabulation will be generated.

In addition, a figure presenting the average in daily change from baseline in BEST Score, 21 days before and 21 days after a PE onset date that meet the protocol definition of PE diagnosis will be plotted. This plot will be presented by treatment group. Only participants with reported exacerbation(s) will be included into the plot. All data of participants with at least one exacerbation will be included when calculating the average in daily change from baseline in BEST Score.

Further, a summary table and a plot will be produced by treatment group where the BEST score will be averaged over a 4-week period. The assignment into the 4-week periods will follow the instructions given in Section 6.7.1.7. The time axis of the figure will be in months.

8.5.2. Duration of Exacerbation Events that Meet the Protocol Definition of PE Diagnosis based on Independent Adjudication Process Over the 52-Week Treatment Period

The average duration of exacerbation events that meet the protocol definition of PE diagnosis over the 52-week treatment period will be included in the analysis (see Section 2). The ITT Analysis Set (see Section 5.2) will be used. The derivation of the endpoint is detailed in Section 6.7.1.

Duration of exacerbation events that meet the protocol definition of PE diagnosis based on independent adjudication process will be summarized by treatment group using descriptive statistics.

[5] Note: Age group is not included into the statistical model as questionnaire is applicable to adult participants only.

8.5.3. Days Hospitalized for Adjudicated PEs per Person-Year Over the 52 Week Treatment Period

The number of days hospitalized for adjudicated PEs per patient year will be presented and will utilize the ITT Analysis Set (see Section 5.2). The derivation of the endpoint is detailed in Section 6.7.1.4.

The number and percentage of participants and the number of hospitalizations, including the duration of hospitalization, the person-time (follow-up time) and the number of days hospitalized per person-year will be summarized descriptively by treatment group.

8.5.4. Days of Absence from Work/School Related to Adjudicated PEs per Patient Year Over the 52-Week Treatment period

The number of days absent from work/school will be presented and will utilize the ITT Analysis Set (see Section 5.2). The derivation of the endpoint is detailed in Section 6.7.1.5.

The number and percentage of participants missing work/school, including the person-time (follow-up time) and the number of days missed per person-year will be summarized descriptively by treatment group.

8.5.5. Change from Baseline in Prebronchodilator and Postbronchodilator FEV_1, FVC, PEFR, $ppFEV_1$ and $FEF_{25-75\%}$ to Weeks 16, 28, 40, and 52

The change from baseline in prebronchodilator and postbronchodilator FEV_1, FVC, PEFR, $ppFEV_1$ and $FEF_{25-75\%}$ to Weeks 16, 28, 40, and 52 will be presented based on the ITT Analysis Set. The derivation of the endpoint is detailed in Section 6.7.3.

Assessments including the changes from baseline will be summarized by time point similar to the display of postbronchodilator FEV_1 in Section 8.3.3.1.

To note: postbronchodilator FEV_1 will be evaluated as part of secondary endpoint analysis in Section 8.3.3.1. Outputs will show prebronchodilator for FEV_1 only.

8.5.6. Outpatient Visits, ER Visits, and Hospitalizations for any Reason

The outpatient visits, ER visits, and hospitalizations for any reason per patient year will be presented and will utilize the ITT Analysis Set (see Section 5.2). The derivation of the endpoint is detailed in Section 6.7.5.8.

The number of outpatient visits, ER visits, duration of hospitalization in days, and hospitalizations for any reason per patient year will be summarized by treatment group using descriptive statistics.

8.5.7. Change in QOL-PCD Domain Scores from Baseline to Weeks 16, 28, 40, and 52 in Adolescent Participants (≥12 to <18 Years of age) with PCD

The change from baseline in QoL-PCD Domain scores at 16, 28, 40, and 52 weeks in adolescents will be presented and will use the ITT Analysis Set.

QoL-PCD Domain scores and changes from baseline will be summarized and statistically analyzed similar to the analysis of QoL-B Respiratory Symptoms Domains score in

Section 8.3.5.1. As adolescents will have data only, the age group will be removed from the statistical model. Completion rates will be presented by time point (see Section 6.7.5.10).

8.5.8. Change from Baseline in EuroQoL-5D-5L Score to Week 52

EuroQoL-5D-5L index score and VAS overall self-rated health status score will be summarized as observed values and changes from baseline at each visit. Changes from baseline will be statistically analyzed similar to the analysis of QoL-B Respiratory Symptoms Domains score in Section 8.3.5.1.

The percentage of participants' categorical responses to each of the 5-dimensions will be tabulated. VAS and index scores and changes from baseline will be summarized and statistically analyzed similar to the data evaluation of postbronchodilator FEV_1 in Section 8.3.3.1. Completion rates will be presented by time point (see Section 6.7.5.10).

8.5.9. Change from Baseline in QoL-B Domain Scores to Weeks 16, 28, 40, and 52 in Adult Participants

The change from baseline in QoL-B Domain scores at Weeks 16, 28, 40, and 52 in which all observed data of adult participants will be included in the analysis and will use The ITT Analysis Set (see Section 5.2).

QoL-B Domain Scores and changes from baseline will be summarized and statistically analyzed by domain like the analysis of QoL-B Respiratory Symptoms Domain Score in Section 8.3.5.1. A separate figure for each domain will be provided. As adult participants will have data only, the age group will be removed from the statistical model.

8.5.10. PGI-C and the Change from Baseline in PGI-S at Weeks 16, 28, 40, and 52 in Adult Participants

The PGI-C and the PGI-S change from baseline in at Weeks 16, 28, 40, 52 in which all observed data will be included in the analysis will be presented and will use the ITT Analysis Set (see Section 5.2).

PGI-S and PGI-C will be summarized by treatment group. PGI-S will be tabulated using a shift from baseline at visits 16, 28, 40, and 52, while PGI-C will be summarized by visit. As adult participants will have data only, the age group will be removed from the statistical model. Completion rates will be presented by time point (see Section 6.7.5.10).

8.5.11. Rate of Change in Prebronchodilator and Postbronchodilator FEV_1 Over the 52-Week Treatment Period

The rate of change in prebronchodilator and postbronchodilator FEV_1 over the 52-Week treatment period in which all observed data will be included in the analysis will be presented and will use the ITT Analysis Set (see Section 5.2) The derivation of the endpoint is detailed in Section 6.7.3.

The rate of change will be summarized descriptively by prebronchodilator and postbronchodilator and displayed by brensocatib dose levels and placebo.

Prebronchodilator and postbronchodilator FEV_1 will each be analyzed using a linear random coefficients model including treatment group as a categorical fixed effect, time (in weeks) as continuous fixed effect, the treatment-by-time interaction, a random time coefficient for subject, and a random intercept for subject. The variance-covariance structure for the random effects will be unstructured. This analysis will be performed in SAS using the MIXED procedure. The OM option will be used to adjust the coefficients for the LSMEANS to reflect the observed data.

The equations for the fitted line for each treatment group will be presented.

Change from baseline values will be displayed along with the regression line in a graph. The actual study day will be used at the time axis.

8.5.12. Change from Baseline in BEST-CT and AA Scores at Week 52

Analysis of CT substudy endpoints will be described in a separate SAP.

8.5.13. Change from Baseline in Concentration of Biomarkers (NE, CatG, PR3) in Sputum to Week 52

Please refer to Section 11.1.

8.5.14. Change from Baseline in Concentration of Biomarkers (NE, CatG, and PR3) in Blood to Week 52

Please refer to Section 11.2.

9. SAFETY

Unless otherwise stated all summaries will have corresponding listings.

Data collected in the safety monitoring (i.e., follow-up after discontinuation of randomized IP) will be analyzed separately, see Section 9.14 for details.

The Safety Analysis Set (see Section 5.3) will be utilized, if not specified otherwise.

9.1. Exposure to IP, Compliance, and IP Interruption

Exposure to IP will be descriptively summarized by treatment group including the below (see Section 6.4.7 for derivation of data points):

- Duration of treatment of IP,
- Duration of treatment with IP by categories[6]:
  - <4 weeks
  - <12 weeks
  - >=12 weeks to <24 weeks
  - >=24 weeks to <36 weeks
  - >=36 weeks to <=52 weeks
  - >52 weeks,
- Cumulative duration of treatment with IP by categories:
  - >=12 weeks,
  - >=24 weeks,
  - >=36 weeks.
- Duration of IP exposure,
- Duration of IP exposure by categories:
  - <4 weeks
  - <12 weeks
  - >=12 weeks to <24 weeks
  - >=24 weeks to <36 weeks
  - >=36 weeks to <=52 weeks
  - >52 weeks,
- Cumulative duration of IP exposure by categories:
  - >=12 weeks,
  - >=24 weeks,
  - >=36 weeks.
- Number and percent of participants compliance to IP, categorized as: >120%, >100-<=120%, >=75-<=100%, <75%,
- Number and percent of participants missed (at least one) IP intake,
- Basic summaries of number of days a participant missed IP intake,
- Number and percent of participants who missed IP due to COVID-19.

[6] The category "<4 weeks" will be a single category for duration of treatment of IP as well as for the duration of IP exposure.

A cross tabulation of IP randomized and IP received (actual received) will be generated by treatment group and dispensed visit, e.g., Day1, Week 4, Week 16, Week 28, and Week 40. The tabulation will count the number of participants as well the number of incorrect doses. The IP received category will separately count randomized but not treated participants.

In addition, the below listings will be produced:

- IP used from specific batches as provided by the interactive response system,
- randomization scheme and codes.

9.2. Adverse Events

The AE verbatim descriptions (Investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to primary SOC and PT using the most recent MedDRA version.

Treatment-emergent adverse event (TEAEs) are those AEs that occurred on or after[7] the date of first dose of IP and within 28 days after the last dose of IP[8]. AEs that occur between the time participant signs the ICF for the study and the time when participant receives his/her first dose of IP on Study Day 1 will be summarized as medical history and not as a TEAE unless the event meets the definition of a serious AE (SAE).

Where AE start dates are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates or the AE end date indicate that the AE started before the first administration of IP (see Table 9).

Table 9: TEAE Assignment in Case of Missing AE Start Date Elements

Missing elements of AE start	Rule (study drug start = first dose of IP)	Classification
Regardless of any missing information for AE start: AE end date < IP start date		non-TEAE
Otherwise (i.e., if AE end date ≥ IP start date)		
- day/month/year	all AEs	TEAE
- day and month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non-TEAE
- day	AE start month/year ≥ IP start month/year	TEAE
	AE start month/year < IP start month/year	non-TEAE

Duration of AEs will be calculated in days (see Section 6.4.5). If date of onset or end date of event is missing, duration will be set to missing.

[7] An AE that begin in screening but worsen during the treatment period will be reported as TEAE as the investigators are asked to enter a new event into the eCRF.
[8] Date of last IP administration will be collected from EOT form where the leading question "*Last dose date*" is recorded.

Tabulations that are displayed by SOC and PT will be ordered by descending order of total incidence of SOC, and PT within each SOC. Tabulations of the following types will be presented:

- Overall incidence of TEAEs including the incidence of participants with at least one:
  - TEAE,
  - serious TEAE,
  - severe TEAE,
  - TEAE resulting in death,
  - TEAE related to IP,
  - serious TEAE related to IP,
  - TEAE of Special Interest (TEAESI),
  - TEAE leading to withdrawal from IP
  - TEAE leading to withdrawal from study, and
  - COVID-19 TEAE; will be identified through PTs as indicated in Appendix K
- Incidence of COVID-19 TEAEs including the incidence of participants with at least one of the below will be presented overall and by months. By months derivation will follow the algorithm used in Section 6.7.1.7. The AE start date will be considered. COVID-19 TEAEs will be identified through PTs as indicated in Appendix K:
  - TEAE,
  - serious TEAE,
  - severe TEAE,
  - TEAE resulting in death,
  - TEAE related to IP,
  - serious TEAE related to IP,
  - TEAE leading to withdrawal from IP, and
  - TEAE leading to withdrawal from study.
- Participant's incidence of TEAEs by MedDRA SOC and PT:
  - TEAEs,
  - severe TEAEs,
  - serious TEAEs,
  - TEAEs related to IP,
  - serious TEAEs related to IP,

  - TEAEs resulting in Death,
  - TEAEs leading to IP withdrawal,
  - TEAEs leading to study withdrawal,
  - COVID-19 TEAEs will be identified through PTs as indicated in Appendix K.
- Participant's incidence of TEAEs by relationship to IP by MedDRA SOC and PT.
- Participant's incidence of TEAEs by MedDRA SOC, PT, and maximum severity. (A participant will be classified at the highest reported severity at PT level. Missing severity will be classified as missing on the summary if there is no non-missing severity at the level of summarization.).
- Participant's incidence of TEAEs by MedDRA PT.
- Correlation between COVID-19 AEs within + 30 days of an exacerbation event that meet the protocol definition of PE diagnosis based on independent adjudication process start and end date; COVID-19 AEs will be identified through PTs as indicated in Appendix K.

For those participants who had at least one serious TEAE, TEAESI, or TEAE leading to withdrawal of IP, all information pertaining to AEs noted during the study will be presented in a participant listing. Non-treatment-emergent AEs will be listed separately.

9.3. Adverse Events of Special Interest

AESIs are defined as events known as related to treatment with DPP1 inhibitors and will be identified through the AE form by looking into the "AESI Category" selected by the investigator. Additional information on AESIs will be collected on dedicated eCRF forms. Tabulations will be prepared for each event type by treatment group:

- Hyperkeratosis,
  - Hyperkeratosis events by severity and signs. Tabulation will be separated to include investigator and dermatologist assessments
  - Hyperkeratosis events by SOC and PT
- Severe Infection
  - by MedDRA SOC and PT
  - Infection-Pneumonia events
  - Severe infections by SOC and PT
- Periodontitis/Gingivitis,
  - the median time from randomization to first referral of a participant. Censoring will not be applied
  - distribution of changes in Patients Pocket Depth (PPD) from first to follow-up periodontitis assessment
  - participants with number of change >=2 and size change >=2 mm in PPD from first to follow-up periodontitis assessment
  - participants with 2 sites of a change >=2 mm and the number of changes >=2 mm in PPD

- dental TEAEs
- distribution of gingival inflammation
- Severe periodontitis/gingivitis events by SOC and PT

A summary of the incidence will be provided for each TEAESI by treatment group. In addition, the risk difference estimate (unadjusted) and the exact 95% confidence interval will be provided for treatment comparison between each brensocatib dose and placebo.

9.4. M8 (Thiocyanate) Toxicity Analysis

To evaluate the impact of brensocatib treatment on AEs that might have potential association with M8 (thiocyanate), including hypothyroidism, hypotension, and neurotoxicity, additional investigations will be made.

The thiocyanate-related AEs will be identified using a hierarchical approach such that MedDRA FDA Medical Queries (FMQs) will be used when available and MedDRA Standardized Medical Queries (SMQs) will be used when an FMQ is unavailable. When an FMQ and SMQ are both unavailable, a Customized Medical Query (CMQ) will be created.

The following thiocyanate-related AEs will be identified.

- FMQs:
  - Hypotension (FMQ grouping: hypotension)
  - Seizures (FMQ grouping: Seizure)
  - Confusion (FMQ grouping: Confusional State)
- SMQs:
  - hypothyroidism (SMQ narrow category: hypothyroidism)
  - delirium (SMQ narrow category: noninfectious encephalopathy/delirium)
- CMQ:
  - Hallucinations
    - (Preferred Terms):
      - Hallucination aggravated
      - Kinesthetic hallucination
      - Organic hallucinosis syndrome
      - Hallucinations
      - Hallucination NOS
      - Sensory hallucinations
      - Drug-induced hallucinosis
      - Hallucinating
      - Stump hallucination

For hypotension, blood pressure will also be investigated for abnormalities defined as:

- Systolic blood pressure <90 mmhg and diastolic blood pressure <60 mmhg, or
- Change from Baseline in systolic and diastolic blood pressure >=30 mmHg,

The number and percentage of participants with an AEs that might have potential association with M8will be presented in an overview table. The M8 concentrations in plasma, when

available, will be described descriptively and changes from baseline until the time point the AE reported the very first time.

9.5. Deaths

A listing of all AEs resulting in death will be provided.

9.6. Subgroup Analyses

Subgroup analyses for adverse events including AESI and M8 metabolite analysis will be reported in the adolescent subgroup (12- <18 years of age).

9.7. Clinical Laboratory Evaluations

Numeric laboratory parameters (hematology, chemistry, and urinalysis) will be summarized using descriptive statistics at baseline and at each post-baseline timepoint. Changes from baseline will also be summarized. Descriptive statistics at baseline and change from baseline is limited to continuous data. Categorical data, e.g., urinalysis, will be tabulated as well. A separate by-participant listing will be provided for abnormal values reported.

Shift tables from baseline to the worst result post-baseline including unscheduled assessments will be provided to assess changes in laboratory values. Worst values are results which have the highest distance to the normal range. Reference ranges established by the central laboratory will be used to determine shifts.

Participants experiencing ALT or AST $\geq 3 \times$ upper limit of normal (ULN) and total bilirubin $> 2 \times$ ULN or ALT or AST $\geq 5 \times$ ULN at any point during the study irrespective of an increase in ALP will be tabulated by treatment group. The elevations do not have to occur at the same time or within a specified time frame. Potential cases will be summarized descriptively and listed. In addition, individual (worst) ratio of ULN post-baseline will be presented graphically.

Arithmetic mean plots of laboratory values over time will be prepared for continues laboratory test. The standard deviation will be included at each sampled time point.

A summary of counts of participants with at least one abnormal laboratory value at any visit including unscheduled will also be provided.

Testing for HBcAb, HBsAb, HBsAg, HIV, and HCV will be conducted at Screening only. Those test results will be summarized and listed.

The number and percentage of participants with potentially clinically significant abnormalities (PCSA) will be summarized as defined in Table 10. For the determination of PCSA unscheduled assessment will be considered.

Table 10: Criteria for Potentially Clinically Significant Abnormalities (PCSA)*

Parameter code	Parameter	PCSA
Clinical Chemistry		
SODIUM	Sodium (mmol/L)	<120.0 mmol/L >155.0 mmol/L
K	Potassium (mmol/L)	<3.0 mmol/L >6.0 mmol/L
MG	Magnesium (mmol/L)	<0.4 mmol/L >1.23 mmol/L
CA	Calcium (mmol/L)	<1.75 mmol/L >3.1 mmol/L
GLUC	Glucose (mmol/L)	<2.2 mmol/L
AST	Aspartate Aminotransferase (U/L)	> (5.0 x ULN) if baseline was normal or > (5.0 x baseline) if baseline was abnormal
ALT	Alanine Aminotransferase (U/L)	> (5.0 x ULN) if baseline was normal or > (5.0 x baseline) if baseline was abnormal
ALP	Alkaline Phosphatase (U/L)	> (5.0 x ULN) if baseline was normal or > (5.0 x baseline) if baseline was abnormal
BILI	Bilirubin, Total (umol/L)	> (3.0 x ULN) if baseline was normal or > (3.0 x baseline) if baseline was abnormal
LDH	Lactate Dehydrogenase (U/L)	> (1.0 x ULN)
CREAT	Creatinine (umol/L)	> (3.0 x ULN) if baseline was normal or > (3.0 x baseline) if baseline was abnormal
CREATCLR	Creatinine Clearance (mL/min/1.73m2)	<29.0 ml/min/1.73 m^2
Hematology		
HGB	Hemoglobin (g/L)	<80.0 g/L Absolute change from baseline >40.0 g/L
WBC	Leukocytes (10^9/L)	<2.0 10^9/L
NEUT	Neutrophils (10^9/L)	<1.0 10^9/L
LYM	Lymphocytes (10^9/L)	<0.5 10^9/L >4.0 10^9/L
PLAT	Platelets (10^9/L)	<50.0 10^9/L
Urinalysis		
UGLUC	Glucose, Urine (mg/dL)	Present
UPROT	Protein, Urine (mg/dL)	<0.0 mg/dL >14.0 mg/dL

9.8. Pregnancy

Pregnancy results from serum or urine pregnancy testing will be listed for all participants.

9.9. Vital Signs and Pulse Oximetry

Systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, height, weight, and BMI will be collected at protocol specified visits.

Descriptive summaries of actual values and changes from baseline will be based on available data and will be provided by visit and treatment group.

Arithmetic mean plots of vital signs and oximetry parameters over time will be prepared. The standard deviation will be included at each sampled time point.

9.10. Electrocardiogram

ECG parameters will be collected at protocol specific visits.

Descriptive summaries of actual values and changes from baseline will be based on available data and will be provided by visit. Investigator and central reading interpretation will be summarized by visit, too.

A categorical summary of QTcF interval will be provided using counts and percentages at baseline and maximum post-baseline by treatment for the following categories:

- Result >450 and ≤480 msec;
- Result >480 and ≤500 msec;
- Result >500 msec;
- Change from Baseline >30 and ≤60 msec;
- Change from Baseline >60 msec.

Safety 12-lead ECG data will be provided in a data listing.

9.11. Physical Examination

Any abnormalities noticed by investigator during the Physical Examination at Screening will be recorded in the medical history, or as an AE if occurred or worsens after ICF.

Dates of Physical Examination will not be listed.

9.12. Prior, Concomitant and Post-IP Medications

The ITT Analysis Set (see Section 5.2) will be used for describing medication usage during the study. Classification of used medications into prior, concomitant or post will be done as detailed in Section 6.4.8.

Prior, concomitant and post medications will be summarized separately. The number and percentage of participants reporting the medication will be presented for participants using at least 1 medication, at least one medication at the Anatomical Therapeutic Class Level 4

(ATC4) level, and by preferred term within ATC4. If ATC Level 4 is not available ATC Level 3 is used instead. If ATC Level 3 is not available ATC Level 2 is used instead.

9.13. Prior, Concomitant and Post-IP Procedures

The ITT Analysis Set (see Section 5.2) will be used for describing the number and percentage of participants undergoing a procedure prior to and during study conduct. Classification of procedures into prior, concomitant, or post-treatment will be done as detailed in Section 6.4.8.

Prior and concomitant procedures will be summarized by SOC and PT using the most recent MedDRA version. Participants are counted only once in each SOC and only once in each PT.

Post-treatment procedures will be listed only, while procedures prior to initiation of this study will be listed as part of participants medical history.

9.14. Summary of Data After Early Discontinuation of IP

All participants are encouraged to stay in the study regardless of IP discontinuation. Any participants who discontinue from IP will have their reason for discontinuing IP recorded and will continue in the study with their remaining scheduled study visits. The eCRF collection of data does not distinguish visits relative to IP termination milestone, therefore for the purpose of the analysis observations will be flagged if collected after IP early discontinuation. An additional timing variable will be introduced to reflect Study Day relative to EOT for visits occurring beyond treatment discontinuation.

Descriptive summaries will be presented for the subgroup of participants who discontinues IP early based on the available data through the EOS visit. For safety parameters these summaries will present data after 28 days following the last IP intake (>EOT+28 days). The summaries will be limited to the following assessments:

- AE, SAEs and AESIs,
- Laboratory and vital signs assessments.
- Deaths will be listed.

9.15. Chest CT Scan for Eligibility

A high-resolution chest CT scan will be performed at the Screening Visit if the participant does not have prior radiological confirmation of NCFBE diagnosis or if the available CT scan was obtained more than 5 years prior to the participants Screening Visit or the existing CT scan cannot be read due to quality issues. Presence of previous scans or date of a new chest CT scan will be listed.

10. PHARMACOKINETIC

The study includes a PK substudy at select sites. The substudy is aimed/designed to include approximately 300 adult participants from whom blood PK will be collected. In addition, blood PK samples will be collected from all adolescent participants and adult participants who enrolled in the main study at selected study visits.

The PK analysis will be based on the Pharmacokinetic Concentration Analysis Set (see Section 5.5) and will include data collected up to the last dose date as steady-state concentrations are of interest. Non-compartmental PK parameters will not be determined in this study.

PK plasma concentrations that are collected outside the acceptable collection windows (see Appendix G) will be flagged in the listing with a footnote that these concentrations are excluded from the concentration summary.

10.1. Brensocatib Plasma Concentration Over Time

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Concentrations for brensocatib will be summarized by brensocatib dose level, day, and nominal timepoint in three separate tables for PK sub-study, adolescent cohort, and main study. In addition, summary table will be repeated for PK Sub-Study participants who are not under cyclic antibiotics therapy.

For summary tables, the number of BLQs and non-BLQs at each scheduled timepoint will be reported. Summary statistics will be calculated for mean, minimum and maximum only if the number of non-BLQ concentrations at a scheduled timepoint is <3 and other summary statistics will be reported as not calculable (NC). Values BLQ will be set to zero for calculation of descriptive statistics.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of participant level concentrations and summary tables of concentration are as follows:

Table 11: Rounding of Plasma Concentration Data in Tables and Listings

Concentration Listings and Tables	Rounding
Individual Concentrations	*n* s.d. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.d. capped at 4
Mean, SD, Median, GM	*n+1* s.d. capped at 4
CV%, gCV%	*1* d.p.
N, n	whole number

s.d. = significant digits, d.p. = decimal place

Concentration Figures:

The below displays will be for participants participating the PK/PD substudy, adolescent cohort and main study (for participants with PK concentration data). According to CSP

Section 8.2 pre-dose blood PK samples will be collected from all participants in the PK/PD substudy and from adolescents for participants on Day 1, Week 4, Week 16, Week 28, Week 40, and Week 52, with an optional 2-hour (±30 minutes) post-dose sample collected at select visits (i.e., Day 1, Week 4, Week 28, and Week 40). For some participants in the main study, PK samples were collected at selected study visits at pre-dose and 2 hours post-dose.

To visualize participant-level concentrations and the comparison between groups for each treatment, the descriptive PK graphs listed below will be generated. LLOQ will be given in a footnote.

- Spaghetti-Plots: Individual participant profiles for plasma concentration data over (actual) time on linear/linear and log/linear scale (log scale for concentration data, time on linear scale) stratified by dose (1 figure per dose level with the individual profiles of the same dose level overlaid) and by groups (PK/PD sub-study, adolescent cohort and main study).
    - BLQ values on Day 1 pre-dose will be set to 0. When using log/linear scale, these values will be considered missing.
    - BLQ values will be set to missing except for Day 1 pre-dose.
- Mean (+SD) profiles for plasma concentration data over (nominal) time on linear/linear and log/linear scale by dose level overlaid in the same figure and by groups (PK/PD sub-study, adolescent cohort and main study).
    - BLQ values will be set to 0. When using log/linear scale, these values will be considered missing.

Figures will be generated using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for the x-axis (i.e., do not use an ordinal scale). Actual sampling time will be used for individual plots while scheduled sampling time will be used for mean plots.

Concentration Listings:

Concentration listings will include nominal PK sampling time, actual sampling times relative to (most recent) dose administration, deviation from nominal time, percent deviation from nominal time, and concentrations. Plasma concentrations below the LLOQ will be presented as BLQ in the listings and the LLOQ value presented as a footnote. There will be 3 separate concentration listings for PK/PD sub-study, adolescent cohort, and main study.

11. PHARMACODYNAMIC

The PK/PD substudy aimed/designed to include approximately 300 evaluable adult participants from whom sputum PD samples will be collected. In a blood PD substudy, NSP blood samples will be collected from approximately 40 of these participants. In addition, sputum PD samples will be collected from all adolescent participants (blood PD samples will not be collected from adolescents). Note, with global protocol amendment 3 (version 6) sputum samples will be collected from all newly enrolled adult participants.

If not stated otherwise, concentration of PD biomarkers (NSP) reported as BLQ will be imputed by LLOQ/2 in all PD data tabulations and plots. LLOQ value will be provided by the laboratory.

The Pharmacodynamic Analysis Sets (see Section 5.4) will be utilized, if not specified otherwise. Derivation of PD Parameters can be found in Section 6.8.

The handling of ICEs for the change in concentration of PD parameters (NE, CatG, and PR3) will follow the On-IP approach (see Section 2).

11.1. Change in Concentration of Biomarkers (NE, CatG, PR3) in Sputum to Week 52

Concentration data of adults from PK/PD substudy, and main study will be pooled together. Data display will be repeated for adolescents.

Baseline and changes from baseline obtained from sputum for NE, CatG, and PR3 will be summarized. Post-baseline parameter values will be natural-log transformed and statistically analyzed similar to the analysis of post-bronchodilator FEV_1 (mL) in Section 8.3.3. In addition, the percentage change from baseline as detailed in Section 6.8 will be summarized.

The observed time to maximum reduction and maximum reduction (see Section 6.8) for NE, CatG, and PR3 will be reported and listed for each participant.

Individual figures of NE, CatG, and PR3 versus actual time will be presented with all participants overlaid on the same plot for each dose level (spaghetti plots). Treatment groups will be differentiated by line patterns.

Arithmetic mean ± SD plots versus nominal time will also be presented with all dose levels for brensocatib and placebo overlaid on the same plot. One plot will be produced for each pharmacodynamic sputum parameter.

In addition, mean of %change (+/- SD) values over time will be produced by parameter using scheduled sampling time by dose level overlaid in the same figure. Further, the %change profiles will be produced over time displaying NE, CatG, and PR3 activities side by side in box plots by treatment group.

11.2. Change in Concentration of Biomarkers (NE, CatG, PR3) in Blood to Week 52

The analysis of concentration of biomarkers in sputum in Section 11.1 will be repeated for concentration of biomarkers in blood, except the statistical analysis which will not be produced due to the limited number of participants.

12. PHARMACOKINETIC AND PHARMACOKINETIC / PHARMACODYNAMIC MODELLING

A stand-alone modeling and simulation analysis plan will be written for the population PK and PK/PD models.

13. CHANGES TO PROTOCOL-PLANNED ANALYSES

- ITT Analysis Set:

CSP, Section 10.2.2	SAP, Section 5.2	Reason
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.	The Intent-to-Treat (ITT) Analysis Set comprises all **participants** who were randomized**, excluding participants from Ukraine and participants from site USA065**. This set will be analyzed using the treatment to which the **participant** was randomized, regardless of the treatment actually received.	To clearly indicate the exclusion of participants from Ukraine and participants from site USA065 in the definition of the ITT Analysis Set. Refer to CSP Section 10 where exclusion of all of the efficacy and safety data that have already been collected from 44 Ukraine participants impacted by the war in Ukraine will be listed only and not included in the formal efficacy and safety analyses. Due to a lack of accountability and responsiveness to the significant GCP non-compliance issues identified at the site USA065 , participants enrolled at the site USA065 will be excluded from any analysis.

- Pharmacodynamic Analysis Sets:

CSP, Section 10.2.4	SAP, Section 5.4	Reason
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.	The PD Analysis Set comprises participants subjects who have consented to participate in the PD substudies, in adolescent cohort and in the main study, have received at least 1 dose of study drug, and have at least 1 predose and 1 postdose measurement of biomarkers, and will exclude participants from Ukraine and participants from site USA065. The PD Analysis Set will be analyzed using the actual treatment received. This study has two sources for PD parameters. This is why the PD analysis set is further differentiated between the below analysis sets. The Blood PD Analysis Set comprises participants who have consented to participate in the PD Blood substudy, have received at least 1 dose of study drug, and have at least 1 pre-dose and 1 post-dose measurement of blood biomarkers, and will exclude participants from Ukraine and participants from site USA065. The Sputum PD Analysis Set comprises participants who have received at least 1 dose of study drug, and have at least 1 predose and 1 postdose measurement of sputum biomarkers, and will exclude participants from Ukraine and participants from site USA065. PD biomarkers are NE, CatG, and PR3, also referred to as neutrophil serine proteases (NSPs). Participants in these Analysis Sets will be used for all PD summaries and statistical analyses.	Differentiation between sputum and blood PD added.

- Pharmacokinetic Concentration Analysis Sets

CSP, Section 10.2.5	SAP, Section 5.5	Reason
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.	The PK Concentration Analysis Set comprises participants who have consented to participate in the PK substudy, in adolescent cohort and in the main study, have received at least 1 dose of brensocatib, and have at least 1 post-dose plasma concentration of brensocatib, excluding participants from Ukraine and participants from site USA065. Participants will be classified according to actual treatment received regardless of the treatment group to which they were randomized.	Clarification added that PK samples of adolescents will be analyzed separately. As indicated for the ITT analysis set, participants from Ukraine and site USA065 will be excluded.

- CSP Section 2.3:

CSP Definition	SAP Definition	Reason
Change in PGI-S and PGI-C from Baseline to Weeks 16, 28, 40, and 52 in adult subjects	PGI-C and the Change from Baseline in PGI-S at Weeks 16, 28, 40, and 52 in Adult Participants	Wording adjusted for clarity. PGI-C already includes the change, a further change from baseline is not required.
Duration of adjudicated PEs over the 52 week treatment period	Duration of ~~adjudicated PEs~~ **exacerbation events that meet the protocol definition of PE diagnosis** Over the 52-Week Treatment Period	To keep consistency in the language of PEs
Change from Baseline in prebronchodilator and postbronchodilator FEV1, FVC, PEFR, ppFEV1, and FEF(25-75%) at Weeks 16, 28, 40, 52, and over 52 weeks	Change from Baseline in prebronchodilator and postbronchodilator FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), percent predicted forced expiratory flow in 1	The benchmark analyses at different timepoints are clinically relevant to evaluate the treatment effect.

	second ($ppFEV_1$) and forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{[25-75\%]}$) at Weeks 16, 28, 40, **and** 52~~, and over 52 weeks~~	
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	Change in QOL-PCD Domain Scores From Baseline to Weeks 16, 28, 40, **and** 52~~, and Over 52 Weeks~~ in Adolescent Participants (≥12 to <18 Years of age) with PCD	The benchmark analyses at different timepoints are clinically relevant to evaluate the treatment effect.
Change in concentration of blood NE, CatG, PR3, and neutrophil functions from Baseline to Week 52	Change in concentration of blood NE, CatG, **and** PR3 ~~and neutrophil functions~~ from Baseline to Week 52	NE, CatG, and PR3 are clinically relevant PD variables.

- CSP Section 5.11:

CSP Definition	SAP Definition	Reason
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.	**Concomitant medications (or procedures) are defined as medications (or procedures) taken between first administration of randomized IP and last randomized IP plus 28 days.**	Concomitant procedures will be determined based on the initiation of first study drug rather than study timing. As an example, any procedures data of participants not receiving IMP should not be tabulated within concomitant procedures.

- CSP Section 10.4.2:

CSP Definition	SAP Definition	Reason
Medical history will be presented in data listings.	**The incidence of medical history abnormalities will be summarized for the ITT and Safety Analysis Set using counts and percentages by System Organ Class (SOC) and Preferred Term (PT).**	Decided to tabulate medical history data in a summary table.

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APPENDIX A. QOL-B SCORING ALGORITHM (VERSION 3.1)

Blue figures: as coded in eCRF

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have lung conditions. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Quality of Life ***Please check the box indicating your answer.***

*During the past **week**, to what extent have you had difficulty:*	A lot of difficulty	Moderate difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as gardening or exercising	☐ 1	☐ 2	☐ 3	☐ 4
2. Walking as fast as others (family, friends, etc.)	☐ 1	☐ 2	☐ 3	☐ 4
3. Carrying heavy things, such as books, groceries, or shopping bags	☐ 1	☐ 2	☐ 3	☐ 4
4. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3	☐ 4

*During the past **week**, indicate how often:*	Always	Often	Sometimes	Never
5. You felt well	☐ 4	☐ 3	☐ 2	☐ 1
6. You felt tired	☐ 1	☐ 2	☐ 3	☐ 4
7. You felt anxious	☐ 1	☐ 2	☐ 3	☐ 4
8. You felt energetic	☐ 4	☐ 3	☐ 2	☐ 1
9. You felt exhausted	☐ 1	☐ 2	☐ 3	☐ 4
10. You felt sad	☐ 1	☐ 2	☐ 3	☐ 4
11. You felt depressed	☐ 1	☐ 2	☐ 3	☐ 4

Continue to Next Page

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Blue figures: as coded in eCRF

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Are you currently on any treatments (such as oral or inhaled medications, PEP or Flutter® device, chest PT, or Vest) for your lung condition?

☐ Yes ☐ No (Go to Question 15 on the next page)

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for your lung condition make your daily life more difficult?
1. Not at all 4
2. A little 3
3. Moderately 2
4. A lot 1

13. How much time do you currently spend each day on your treatments for your lung condition?
1. A lot 1
2. A moderate amount 2
3. A little 3
4. Almost none 4

14. How difficult is it for you to fit in your treatments for your lung condition each day?
1. Not at all 4
2. A little 3
3. Moderately 2
4. Very 1

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?
1. Excellent 4
2. Good 3
3. Fair 2
4. Poor 1

Continue to Next Page

 QOL-B, Version 3.1 Page 2

Blue figures: as coded in eCRF

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Please select a box indicating your answer.

*Thinking about your health during the past **week**, indicate the extent to which each sentence is true for you.*

	Completely true	Mostly true	A little true	Not at all true	
16. I have to limit vigorous activities, such as walking or exercising	☐ 1	☐ 2	☐ 3	☐ 4	
17. I have to stay at home more than I want to	☐ 1	☐ 2	☐ 3	☐ 4	
18. I am worried about being exposed to others who are sick	☐ 1	☐ 2	☐ 3	☐ 4	Doesn't apply
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. I lead a normal life	☐ 4	☐ 3	☐ 2	☐ 1	
21. I am concerned that my health will get worse	☐ 1	☐ 2	☐ 3	☐ 4	
22. I think my coughing bothers others	☐ 1	☐ 2	☐ 3	☐ 4	
23. I often feel lonely	☐ 1	☐ 2	☐ 3	☐ 4	
24. I feel healthy	☐ 4	☐ 3	☐ 2	☐ 1	
25. It is difficult to make plans for the future (vacation, attending family events, etc.)	☐ 1	☐ 2	☐ 3	☐ 4	
26. I feel embarrassed when I am coughing	☐ 1	☐ 2	☐ 3	☐ 4	

Please circle the number or check the box indicating your answer.

*During the past **week**:*

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?
    1. You have had no trouble keeping up 4
    2. You have managed to keep up but it's been difficult 3
    3. You have been behind 2
    4. You have not been able to do these activities at all 1

	Always	Often	Sometimes	Never
28. How often does your lung condition get in the way of meeting your work, household, family, or personal goals?	☐ 1	☐ 2	☐ 3	☐ 4

Continue to Next Page

 QOL-B, Version 3.1 Page 3

Blue figures: as coded in eCRF

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Section II. Respiratory Symptoms

Please check the box indicating your answer.

Indicate how you have been feeling during the past week:	A lot	A moderate amount	A little	Not at all
29. Have you felt congestion in your chest?	☐ 1	☐ 2	☐ 3	☐ 4
30. Have you been coughing during the day?	☐ 1	☐ 2	☐ 3	☐ 4
31. Have you had to cough up mucus?	☐ 1	☐ 2	☐ 3	☐ 4

32. Has your sputum been mostly:
4 ☐ Clear 3 ☐ Clear to yellow 2 ☐ Yellowish-green
1 ☐ Brownish-dark 00 ☐ Green with traces of blood 0 ☐ Don't know

How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath with greater activity, such as housework or yardwork?	☐ 1	☐ 2	☐ 3	☐ 4
34. Have you been wheezing?	☐ 1	☐ 2	☐ 3	☐ 4
35. Have you had chest pain?	☐ 1	☐ 2	☐ 3	☐ 4
36. Have you had shortness of breath when talking?	☐ 1	☐ 2	☐ 3	☐ 4
37. Have you woken up during the night because you were coughing?	☐ 1	☐ 2	☐ 3	☐ 4

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

 QOL-B, Version 3.1 Page 4

Calculation of domain scores

Each of the 37 items is scored from 1 to 4 with higher scores representing fewer symptoms or better functioning and quality of life. The CRF of this study is built in a way, that reverse coding is applied already and is not necessary as detailed in (Quittner, 2015).

The coding of social functioning score and the respiratory symptoms is not correct in the CRF. That is why the score is re-calculated programmatically. Before re-calculating the scale scores for social functioning and the respiratory symptoms, the following preparations are necessary:

- If item 32 = 00 (Green with traces of blood) then item 32 = 1
- If item 32 = 0 (Don't know) then item 32 is set to missing
- If item 19 = 5 (Doesn't apply) then item 19 is set to missing

To note, all domain scores will be re-calculated given the below algorithm.

Scale scores

Each of the 8 domain scores is standardized on a 0 to 100-point scale with higher scores representing fewer symptoms or better functioning and quality of life.

Scale scores are derived from a subset of items and calculated by

$$scale\ score = \frac{mean\ of\ responses - 1}{3} * 100$$

Contributing items:

Table 12: QoL-B Items Contributing to Domain Score Calculation

Domain	#items	Contributing items	Allowed #missing items*
Physical Functioning	5	1, 2, 3, 4, 16	2
Role Functioning	5	17, 20, 25, 27, 28	2
Vitality	3	6, 8, 9	1
Emotional Functioning	4	7, 10, 11, 23	2
Social Functioning	4	18, 19, 22, 26	2
Treatment Burden	3	12, 13, 14	1
Health Perceptions	4	5, 15, 21, 24	2
Respiratory Symptoms	9	29 to 37	4

*If more missing items are observed than allowed, the domain will not be scored.

APPENDIX B. QOL-PCD ADOLESCENT (13-17 YEARS) SCORING ALGORITHM (VERSION 2.0)

Blue figures: as coded in eCRF; blue box: items to be re-coded

QOL-PCD QUESTIONNAIRE Adolescents Ages 13 to 17 years

Section I. Quality of Life

Please check the box indicating your answer.

During the past week, to what extent have you had difficulty:	A lot of difficulty	Some difficulty	A little difficulty	No difficulty
1. Performing activities such as running or playing sports	☐ 1	☐ 2	☐ 3	☐ 4
2. Walking as fast as others	☐ 1	☐ 2	☐ 3	☐ 4
3. Climbing stairs as fast as others	☐ 1	☐ 2	☐ 3	☐ 4

During the past week, indicate how often:	Always	Often	Sometimes	Never
4. You felt well	☐ 1	☐ 2	☐ 3	☐ 4
5. You felt worried about getting sick	☐ 1	☐ 2	☐ 3	☐ 4
6. You felt happy	☐ 1	☐ 2	☐ 3	☐ 4
7. You felt tired	☐ 1	☐ 2	☐ 3	☐ 4
8. You felt energetic	☐ 1	☐ 2	☐ 3	☐ 4
9. You felt exhausted	☐ 1	☐ 2	☐ 3	☐ 4
10. You felt sad	☐ 1	☐ 2	☐ 3	☐ 4
11. Your treatments for PCD got in the way of your activities	☐ 1	☐ 2	☐ 3	☐ 4
12. Doing your treatments frustrated you	☐ 1	☐ 2	☐ 3	☐ 4

Thinking about the state of your health over the last week:

13. How difficult is it for you to fit in your treatments (including medications) each day?
    1. Not at all 4
    2. A little 3
    3. Moderately 2
    4. Very 1

re-coding not needed as correctly done at CRF

QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Please select a box indicating your answer.

*Thinking about your health **during the past week**, indicate the extent to which each sentence is true or false for you.*	Very True	Mostly True	Somewhat True	Not At All True
14. I have trouble recovering after physical effort	☐ 1	☐ 2	☐ 3	☐ 4
15. I have to limit activities such as running or playing sports	☐ 1	☐ 2	☐ 3	☐ 4
16. I feel comfortable discussing my illness with others	☐ 1	☐ 2	☐ 3	☐ 4
17. I feel comfortable blowing my nose in front of friends	☐ 1	☐ 2	☐ 3	☐ 4
18. People are afraid I might get them sick	☐ 1	☐ 2	☐ 3	☐ 4
19. I think my coughing bothers others	☐ 1	☐ 2	☐ 3	☐ 4
20. It is difficult to make plans for the future (for example, going on in school, getting a job, etc.)	☐ 1	☐ 2	☐ 3	☐ 4

Section II. School, Work, or Daily Activities

21. How often were you absent from school, work, or unable to complete daily activities during the past week because of your illness or treatments?

☐ Always 1 ☐ Often 2 ☐ Sometimes 3 ☐ Never 4

22. To what extent does PCD get in the way of meeting school, work, or your own goals?

☐ A lot 1 ☐ Moderately 2 ☐ A little 3 ☐ Not at all 4

QOL-PCD QUESTIONNAIRE

Adolescents Ages 13 to 17 years

Section III. Symptoms

Please select a box indicating your answer.

Indicate how you have been feeling during the past week.	A great deal	Somewhat	A little	Not at all
23. Have you been congested in the chest?	☐ 1	☐ 2	☐ 3	☐ 4
24. Have you been coughing during the day?	☐ 1	☐ 2	☐ 3	☐ 4
25. Have you had to cough up mucus (including swallowing it)?	☐ 1	☐ 2	☐ 3	☐ 4 If not at all go to Question 27

During the past week:

26. Has your mucus been mostly:
☐ Clear 1 ☐ Clear to yellow 2 ☐ Yellowish-green 3
☐ Greenish 4 ☐ Green with traces of blood 5 ☐ Don't know 6

	A great deal	Somewhat	A little	Not at all
27. You had fluid coming out of your ears	☐ 1	☐ 2	☐ 3	☐ 4
28. You had trouble hearing (if you wear hearing aids: you had trouble hearing without your aids)	☐ 1	☐ 2	☐ 3	☐ 4
29. You felt snot dripping down your throat	☐ 1	☐ 2	☐ 3	☐ 4

During the past week, indicate how often:	Always	Often	Sometimes	Never
30. Your breathing has been noisy (whistling, wheezy chest)	☐ 1	☐ 2	☐ 3	☐ 4
31. You had a stuffy nose	☐ 1	☐ 2	☐ 3	☐ 4
32. You had difficulty sleeping because of your chest	☐ 1	☐ 2	☐ 3	☐ 4
33. You had trouble breathing	☐ 1	☐ 2	☐ 3	☐ 4
34. Your ears hurt	☐ 1	☐ 2	☐ 3	☐ 4
35. You had a runny nose	☐ 1	☐ 2	☐ 3	☐ 4
36. You had difficulty sleeping because your nose was blocked up	☐ 1	☐ 2	☐ 3	☐ 4
37. Your ears were blocked up	☐ 1	☐ 2	☐ 3	☐ 4
38. You had a headache	☐ 1	☐ 2	☐ 3	☐ 4

Calculation of domain scores

Each of the 38 items is scored from 1 to 4, except item #26 which is score from 1 to 6, with higher scores representing fewer symptoms or better functioning and quality of life. The CRF of this study is partly designed that reverse coding is applied and is not necessary for all items as detailed in the "*General Hand Scoring Instructions*" for the QOL-PCD Adolescent Version 2 questionnaire. Please check the questionnaire items above. Each item highlighted in blue bar will require reverse coding.

Before calculating the scale scores, the following preparations are necessary:

- If item 25 = 4 (Not at all) then item 26 is set to missing
- If item 26 = 6 (Don't know) then item 26 is set to missing

Scale scores

Each of the 9 domain scores is standardized on a 0 to 100-point scale with higher scores representing fewer symptoms or better functioning and quality of life.

Scale scores are derived from a subset of items and calculated by

$$scale\ score = \frac{sum\ of\ responses - minimum\ possible\ sum\ (n * 1)}{maximum\ possible\ sum\ (n * 4) - minimum\ possible\ sum\ (n * 1)} * 100$$

While n is equal to the number of items (questions) in the respective scale. Contributing items are given in Table 13 below:

Table 13: QoL-PCD Items Contributing to Domain Score Calculation

Domain	#items	Contributing items	Allowed #missing items*
Physical Functioning	5	1, 2, 3, 14, 15	2
Emotional Functioning	4	4*, 5, 6*, 10	2
Treatment Burden	3	11, 12, 13*	1
Role	3	20, 21, 22	1
Social Functioning	4	16*, 17*,18, 19	2
Vitality	3	7, 8*, 9	1
Upper Respiratory Symptoms	5	29, 31, 35, 36,38	2
Lower Respiratory Symptoms	7	23, 24, 25, 26*, 30, 32, 33	3
Hearing Symptoms	4	27, 28, 34, 37	2

*If more missing items are observed than allowed, the domain will not be scored.

Example: For a scale compromising four items (n=4), such as the Emotional Functioning scale, the calculation method is for a participant who obtains 7 points (e.g., 2 points for item #4, 2 points for item #5, 2 points for item #6, and 1 point for item #10):

$$scale\ score = \frac{7 - (4 * 1)}{(4 * 4) - (4 * 1)} * 100 = 25$$

APPENDIX C. QOL-PCD CHILD (12 YEARS) SCORING ALGORITHM (VERSION 2.0)

Blue figures: as coded in eCRF; blue box: items to be re-coded

QOL-PCD QUESTIONNAIRE Children Ages 6-12 years

Please check the box matching your response.

In the past **week**:	Very True	Mostly True	A little bit True	Not at all True
1. You were able to walk as fast as others	☐ 1	☐ 2	☐ 3	☐ 4
2. You were able to climb stairs as fast as others	☐ 1	☐ 2	☐ 3	☐ 4
3. You were able to run, jump, and climb as you wanted	☐ 1	☐ 2	☐ 3	☐ 4
4. You were able to run as quickly and as long as others	☐ 1	☐ 2	☐ 3	☐ 4
5. You were able to do sports that you enjoy (e.g., soccer, dancing or others)	☐ 1	☐ 2	☐ 3	☐ 4

Please check the box matching your response.

And during this past **week**, indicate how often:	Always	Often	Sometimes	Never
6. You felt mad	☐ 1	☐ 2	☐ 3	☐ 4
7. You felt grumpy	☐ 1	☐ 2	☐ 3	☐ 4
8. You felt worried about getting sick	☐ 1	☐ 2	☐ 3	☐ 4
9. You felt sad	☐ 1	☐ 2	☐ 3	☐ 4
10. You felt frustrated about doing your daily treatments	☐ 1	☐ 2	☐ 3	☐ 4
11. You had to stop having fun to do your treatments	☐ 1	☐ 2	☐ 3	☐ 4

QOL-PCD QUESTIONNAIRE Children Ages 6 to 12 years

Please check the box matching your response.

During the past **week**:	Very True	Mostly True	A little bit True	Not at all True
12. You were late or missed school because of PCD	☐ 1	☐ 2	☐ 3	☐ 4
13. You had enough time to do all of your treatments	☐ 1	☐ 2	☐ 3	☐ 4
14. Doing treatments in front of your friends bothers you	☐ 1	☐ 2	☐ 3	☐ 4
15. You spent a lot of time with your friends	☐ 1	☐ 2	☐ 3	☐ 4
16. You missed going to after-school activities because of PCD	☐ 1	☐ 2	☐ 3	☐ 4
17. You were teased by other children because your nose was runny	☐ 1	☐ 2	☐ 3	☐ 4
18. Others were afraid you would get them sick	☐ 1	☐ 2	☐ 3	☐ 4
19. You had trouble hearing (if you wear hearing aids: you had trouble hearing without your aids)	☐ 1	☐ 2	☐ 3	☐ 4
20. Doing your treatments bothered you	☐ 1	☐ 2	☐ 3	☐ 4
21. Your ears felt blocked up	☐ 1	☐ 2	☐ 3	☐ 4

Please check the box matching your response.

Let us know how often in the past **week**:	Always	Often	Sometimes	Never
22. You coughed during the day	☐1	☐ 2	☐ 3	☐ 4
23. Your ears hurt	☐1	☐ 2	☐ 3	☐ 4
24. You woke up during the night because you were coughing	☐1	☐ 2	☐ 3	☐ 4
25. You had to cough up mucus (even if you swallow it)	☐1	☐ 2	☐ 3	☐ 4

QOL-PCD QUESTIONNAIRE **Children Ages 6 to 12 years**

Let us know how often in the past **week**:	Always	Often	Sometimes	Never
26. You had trouble breathing	☐ 1	☐ 2	☐ 3	☐ 4
27. You had liquid coming out of your ears	☐ 1	☐ 2	☐ 3	☐ 4
28. You woke up during the night because your nose was blocked up	☐ 1	☐ 2	☐ 3	☐ 4
29. Your chest hurt	☐ 1	☐ 2	☐ 3	☐ 4
30. You had mucus stuck in your chest	☐ 1	☐ 2	☐ 3	☐ 4
31. You had a runny nose	☐ 1	☐ 2	☐ 3	☐ 4
32. Your head hurt (near your eyes or in your forehead)	☐ 1	☐ 2	☐ 3	☐ 4
33. Your nose felt blocked up	☐ 1	☐ 2	☐ 3	☐ 4
34. You felt snot (stuff) dripping down your throat	☐ 1	☐ 2	☐ 3	☐ 4

Handling of missing items and calculation of the domain scores are detailed in the below table. Calculation of the score is identical to adolescents as detailed in Appendix B.

Table 14: QoL-PCD Child Items Contributing to Domain Score Calculation

Domain	#items	Contributing items	Allowed #missing items+
Physical Functioning	5	1*, 2*, 3*, 4*, 5*	2
Emotional Functioning	4	6, 7, 8, 9	2
Treatment Burden	5	10, 11, 13*, 14, 20	2
Social Functioning	5	12, 15*, 16, 17,18	2
Upper Respiratory Symptoms	5	28, 31, 32, 33, 34	2
Lower Respiratory Symptoms	6	22, 24, 25, 26, 29, 30	3
Hearing Symptoms	4	19, 21, 23, 27	2

+If more missing items are observed than allowed, the domain will not be scored.
*Reverse coding: 1=4, 2=3, 3=2, 4=1

APPENDIX D. QOL-PCD PARENT/CAREGIVERS (CHILDREN AGES 6 TO 12 YEARS) SCORING ALGORITHM (VERSION 2.0)

Blue figures: as coded in eCRF; blue box: items to be re-coded

QOL-PCD QuestionnaireParents/Caregivers (Children Ages 6 to 12)

Section I. Quality of Life

Please indicate how your child has been feeling during the past week by checking the box matching your response.

To what extent has your child had difficulty:

	A lot of difficulty	Some difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as running or playing sports	☐ 1	☐ 2	☐ 3	☐ 4
2. Walking as fast as others	☐ 1	☐ 2	☐ 3	☐ 4
3. Climbing stairs as fast as others	☐ 1	☐ 2	☐ 3	☐ 4
4. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3	☐ 4

During the past week, indicate how often your child:

	Always	Often	Sometimes	Never
5. Seemed happy	☐ 1	☐ 2	☐ 3	☐ 4
6. Seemed worried about his/her illness	☐ 1	☐ 2	☐ 3	☐ 4
7. Seemed tired	☐ 1	☐ 2	☐ 3	☐ 4
8. Seemed well	☐ 1	☐ 2	☐ 3	☐ 4
9. Seemed energetic	☐ 1	☐ 2	☐ 3	☐ 4
10. Was absent or late for school or other activities because of his/her illness or treatments				
11. Was frustrated by doing his/her treatments	☐ 1	☐ 2	☐ 3	☐ 4

Please check the box that matches your response to these questions.

Thinking about your child's state of health during the past week, indicate the extent to which each sentence is true or false for your child:

	Very true	Mostly true	Somewhat True	Not at all True
12. My child had trouble recovering after physical effort	☐ 1	☐ 2	☐ 3	☐ 4
13. Mealtimes were a struggle	☐ 1	☐ 2	☐ 3	☐ 4
14. My child's treatments got in the way of his/her activities	☐ 1	☐ 2	☐ 3	☐ 4
15. My child felt healthy	☐ 1	☐ 2	☐ 3	☐ 4
16. My child got enough help in his/her classroom to perform well (e.g., sitting up front, time to make up homework when sick)	☐ 1	☐ 2	☐ 3	☐ 4
17. My child was able to keep up with his/her school work or outdoor activities	☐ 1	☐ 2	☐ 3	☐ 4
18. My child spent a lot of time on his/her treatments everyday	☐ 1	☐ 2	☐ 3	☐ 4

QOL-PCD QuestionnaireParents/Caregivers (Children Ages 6 to 12)

Please circle the number indicating your answer. Please choose only one answer for each question.

19. How difficult is it for your child to fit in his/her treatments (including medications) each day?

1 1. Not at all
2 2. A little
3 3. Moderately
4 4. Very

20. How do you think your child's health is now?

1 1. Excellent
2 2. Good
3 3. Fair
4 4. Poor

Section II. Symptoms

Please indicate how your child has been feeling during the past week.

	A great deal	Somewhat	A little	Not at all
21. My child had trouble gaining weight	1 ☐	2 ☐	3 ☐	4 ☐
22. My child's ears hurt	1 ☐	2 ☐	3 ☐	4 ☐
23. My child's chest was congested	1 ☐	2 ☐	3 ☐	4 ☐
24. My child coughed during the day	1 ☐	2 ☐	3 ☐	4 ☐
25. My child had to cough up mucus (including swallowing it)	1 ☐	2 ☐	3 ☐	4 ☐
26. My child had a runny nose	1 ☐	2 ☐	3 ☐	4 ☐
27. My child felt mucus dripping down his/her throat	1 ☐	2 ☐	3 ☐	4 ☐

During the past week:	Always	Often	Sometimes	Never
28. My child had trouble hearing (if aided, he/she had trouble without aids)	1 ☐	2 ☐	3 ☐	4 ☐
29. My child had fluid draining from his/her ears	1 ☐	2 ☐	3 ☐	4 ☐
30. My child had a sinus headache	1 ☐	2 ☐	3 ☐	4 ☐
31. My child had trouble breathing	1 ☐	2 ☐	3 ☐	4 ☐
32. My child woke up during the night because he/she was coughing	1 ☐	2 ☐	3 ☐	4 ☐
33. My child had a stuffy nose	1 ☐	2 ☐	3 ☐	4 ☐
34. My child's chest hurt	1 ☐	2 ☐	3 ☐	4 ☐
35. My child had a poor appetite	1 ☐	2 ☐	3 ☐	4 ☐

Handling of missing items and calculation of the domain scores are detailed in the below table. Calculation of the score is identical to adolescents as detailed in Appendix B.

Table 15: QoL-PCD Patent/Caregiver Items Contributing to Domain Score Calculation

Domain	#items	Contributing items	Allowed #missing items+
Physical Functioning	5	1, 2, 3, 4, 12	2
Emotional Functioning	3	5*, 7, 9*	1
Treatment Burden	4	11, 14, 18, 19*	2
Social Functioning	3	10, 16*, 17*	1
Eating and Weight	3	13, 21, 35	1
Health Perception	4	6, 8*, 15*, 20*	2
Upper Respiratory Symptoms	4	26, 27, 30, 33	2
Lower Respiratory Symptoms	6	23, 24, 25, 31, 32, 34	3
Hearing Symptoms	3	22, 28, 29	1

+If more missing items are observed than allowed, the domain will not be scored.
*Reverse coding: 1=4, 2=3, 3=2, 4=1

APPENDIX E. BRONCHIECTASIS EXACERBATION AND SYMPTOM TOOL

Symptoms reported using the BEST diary consists of 6 symptoms: breathlessness, fatigue, sputum volume, sputum color, cough, and cold and flu symptoms. Total possible BEST score for all symptom ratings ranges from 0 to 26. Participants were asked to complete the BEST questionnaire (in the evening) on an electronic diary DAILY from the Screening Visit through EOS Visit (Week 56).

The calculation of the BEST score is the sum of symptom responses, e.g., 1+1+1+1+1+1=6 for responses: "*Breathless when hurrying or walking up a hill*", "*I feel a little tired*", "*Less than a teaspoon*", "*White*", "*Mild*" and "*Sore throat, sore muscle, or runny nose*". If 50% or more of symptom responses are missing, e.g., 3 or more, the BEST score will not be calculated.

Table 16: BEST Items Contributing to BEST Score Calculation

Breathlessness		**Fatigue**	
0	None or rarely	0	I do not feel tired
1	Breathless when hurrying or walking up a hill	1	I feel a little tired
2	Have to walk slowly on level ground or stop for breath after a few minutes on level ground	2	I feel tired but can still do the things I would like to do
3	Can walk less than 100m or a few minutes on level ground before having to stop	3	Tiredness is stopping me from doing things I want to do
4	Breathless when washing or dressing	4	I am so tired I am unable to carry my usual daily activities
Sputum Volume		**Sputum Color**	
0	No sputum	0	No sputum
1	Less than a teaspoon	1	White
2	Teaspoon to an egg-cup	2	Yellow
3	Egg-cup to a cup	3	Green
4	More than a cup	4	Dark Green
5	---	5	Blood stained
Cough		**Cold and Flu Symptoms**	
0	None	0	None
1	Mild	1	Sore throat, sore muscle, or runny nose
2	Moderate	2	Fever/high temperature
3	Severe	3	---
4	Very severe	4	---
5	---	5	I feel like I have an infection

APPENDIX F. EQ-5D-5L SCORING ALGORITHM

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state, where a higher score corresponds to a worse health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

https://euroqol.org/wp-content/uploads/2020/12/UK_crosswalk_SAS.txt

A sample copy of the EQ-5D-5L can be found on the next pages.

Figure 1/ UK (English) EQ-5D-5L Paper Self-Complete (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

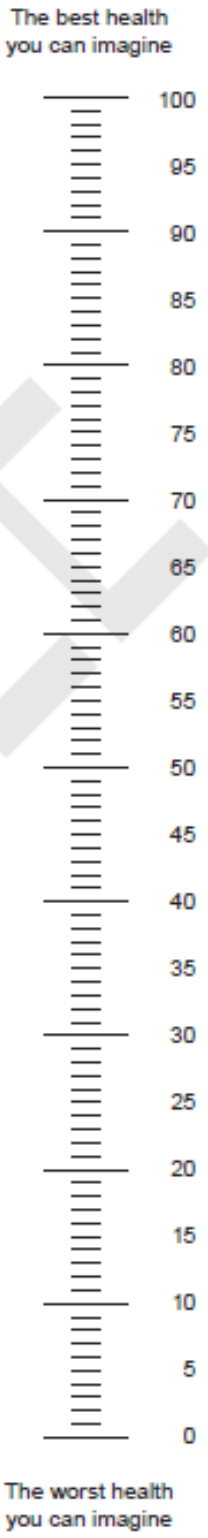
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX G. SCHEDULE OF PHARMACOKINETIC SAMPLE COLLECTION

The details of the blood PK sampling scheme are described in the table below.

Pharmacokinetic blood samples will be collected from all adult participants who participate in the PK/PD substudy and all adolescent participants enrolled in the study.

Table 17: PK sample collection schedule

Day/Week	Collection Time	Collection Window	All Adult Participants	Substudy Participants[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 participants who participate in the PK/PD substudy, and PK blood samples will be collected from all adolescent participants enrolled in the study. The PK/PD substudy will include participants 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 participants will be used for the substudy when substudy sample collection is scheduled at the same timepoint (no extra samples will be collected).

APPENDIX H. SCHEDULE OF PHARMACODYNAMIC SAMPLE COLLECTION

The details of the PD sampling scheme are described in the table below.

Table 18: PD sample collection schedule

Day/Week	Collection Time	All Adult Participants[a]	Substudy Participants [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 participants as introduced with global protocol amendment 3.
b The PK/PD substudy will include participants who are not receiving cyclic antibiotics at Baseline.
c PD blood samples will be collected from approximately 40 adult participants enrolled in the PK/PD substudy at select sites in the United States.
d PD sputum samples will be collected from all adult participants enrolled in the PK/PD substudy. Sputum samples will also be collected from all adolescent participants who are enrolled in the study and are able to produce a sputum sample.
Note: The sputum sample collected for all participants will be used for the substudy when substudy sample collection is scheduled at the same timepoint (no extra samples will be collected).

APPENDIX I. TECHNICAL DETAILS FOR STATISTICAL ANALYSIS

Primary Endpoint: Main Analysis

```
PROC GENMOD DATA=<dataIn> ORDER=DATA;
  CLASS usubjid trtp(REF="Placebo") region1 numpes psaecol agegr3;
  MODEL count = trtp region1 numpes psaecol agegr3
        / OFFSET=ln_fup DIST=NB LINK=LOG WALD TYPE3 NOINT;
  REPEATED SUBJECT=usubjid / TYPE=UNSTR COVB;
  LSMEANS trtp /exp OM;
  ESTIMATE 'brensocatib 10 vs placebo' trt 1 0 -1 / EXP E;
  ESTIMATE 'brensocatib 25 vs placebo' trt 0 1 -1 / EXP E;
  ODS OUTPUT ESTIMATES          =
             CONVERGENCESTATUS  =
             LSMEANS            =
  ;
RUN;
```

Where:

trtp	participants treatment (brensocatib 25mg, brensocatib 10mg, placebo)
region1	stratification factor: North America, Europe, Japan, and the Rest of the World
psaecol	stratification factor: sputum sample being classified as positive or negative for Pseudomonas aeruginosa at screening visit
numpes	stratification factor: number of prior PEs [<3 or ≥3] in the previous 12 months
agegr3	age group: adult, adolescent)
count	number of observed PEs
ln_fup	logarithm of participants time at risk (years)

Sorting: data will be sorted by usubjid

Primary Endpoint: Annualized Rate of Pulmonary Exacerbations– Tipping Point (Sensitivity Analysis)

Participants may discontinue from the study prior to the end of the 52 weeks treatment period, so that the number of PEs after discontinuation is unknown. Table 19 splits the number of events and participants time at risk into two periods, the observed period (Period 1), and the unknown period (Period 2). According to Section 6.7.1 a participant will not be at risk in the days from the start to the end of a PE. Therefore, the sum of periods T1 and T2 might be smaller than the protocol specified treatment period of 52 weeks.

Table 19: Differentiation of Events and Duration for Participants with missing Follow-up Time

Period:	Period 1	Period 2	Total (52 weeks)
Status:	Patient is on-study (PEs are observed)	Patient is off study (PEs not observed)	

Duration (years) followed:	T1	T2	T = T1 + T2
Number of PEs within the period:	Y_1, Y_{obs}	Y_2, Y_{mis}	Y = Y1 + Y2

T1 and Y1 are known, T2 and Y2 are unknown. T will be set to 1 for participants who discontinue from the study early..
T1>0, T2≥0. If T2=0, then Y2=0 and there is no missing data for the corresponding participant.
T2 = 1 − T1

Assumptions for modelling the number of PEs

- For the number of PEs a negative binomial distribution is assumed, which can be fitted with PROC GENMOD using a loglinear model to estimate the parameters θ_1 (regression coefficients β for treatment arms and for covariates and dispersion parameter c).
- The imputation will assume the same patient effect in Periods 1 and 2.
- The unobserved events Y_2 conditional on Y_1 will be imputed from the negative binomial distribution with, using the SAS language for the RAND function, number of successes k^* and probability of success p^*:

  $k^* = \frac{1}{c} + Y_1$ and $p^* = \left(\frac{1}{c} + \psi_1\right) / \left(\frac{1}{c} + \psi_1 + \psi_2\right)$

  where:

  $\psi_1 = T_1 * EXP(x^T\beta)$ and $\psi_2 = T_2 * EXP(x^T\beta)$

  as described by (Keene et al., 2014).
- Simulated PEs will have a duration of 0 days for simplification.
- The negative binomial model is used to analyze the observed data in period 1 and the imputed datasets with period 1+2 data.

MI under MAR assumption: (e.g., Schafer, 1999)

Within the MI approach the missing data is imputed multiple times using the following two steps:

- **Step 1:** Simulate the parameters θ_1 from the posterior distribution, given the observed data Y_{Obs}.
- **Step 2:** Simulate the missing data from the conditional distribution of missing data, given the simulated parameters from Step 1 and the observed data:

$$Y_{mis} \sim P(Y_{mis}|Y_{obs}, \theta_1)$$

Each imputed dataset is analyzed with PROC GENMOD. Results are combined with PROC MIANALYZE.

Tipping point analysis under MNAR assumptions:

For a tipping point analysis, the MI approach is modified: After Step 1 the parameter ψ_2 is adjusted, reducing treatment effects before imputing the missing data in Step 2. Thus, imputations are done assuming smaller treatment effects in the missing data, and it can be checked which decrease in treatment effects would change a significant result into a non-significant result.

The analysis of imputed datasets with PROC GENMOD and the combined analysis with PROC MIANALYZE remain unchanged, only the imputations in Step 2 are modified under the assumption of reduced treatment effects.

Computations for Step 1:

Samples from the posterior distribution can be drawn with the BAYES statement in PROC GENMOD based on only the observed data, which applies an iterative algorithm. After a sufficient number of "burn-in" iterations (`NBI=200`), an appropriate number of samples from the posterior distribution are simulated (`NMC=100`) and can be saved into a dataset:

```
*--- GENMOD ---;

PROC GENMOD DATA=_16keepTrt;
  CLASS trtp(REF="Placebo") REGION1(REF="North America") NUMPES(REF=">=3")
PSAECOL(REF="Negative") AGEGR3(REF="Adult");;
  MODEL aval = trtp region1 psaecol numpe3 agegr3 / OFFSET=ln_timeAtRisk
DIST=NB
               LINK=LOG WALD TYPE3;
  BAYES NBI=200 NMC=100 THINNING=1 SEED=351985287
    OUTPOST=_25bayes SAMPLING=GAMERMAN PLOTS=ALL DIAGNOSTICS=NONE
    COEFFPRIOR=UNIFORM
    DISPERSIONPRIOR=GAMMA(SHAPE=0.0001,ISCALE=0.0001);
RUN;
```

```
*--- Merge posterior samples with observed data ---;

PROC SQL;
  CREATE TABLE _40join AS
    SELECT *
      FROM _16keepTrt, _25bayes
  ORDER BY _imputation_, usubjid
  ;
QUIT;
```

The above statements simulate 100 values of $\theta_1 = (\beta, c)$ in dataset `_25bayes` given the observed data on PEs which can then be used in Step 2 to create 100 imputed datasets. Further, ψ_1 and ψ_2 can be calculated and the dispersion parameter c obtained at the same time.

The values for θ_1 in row k of `_25bayes` are used to impute the missing values in the k-th imputed dataset.

Computations for Step 2:

For Step 2 the unknown value Y_2 has to be sampled from the conditional distribution given the observed values (Y_1, T_1) and the generated parameters from step 1.

SAS-Code:

```
      Y2 = RAND('NEGBINOMIAL', P_STAR, K_STAR);
```

Each imputed dataset is then analyzed with PROC GENMOD based on the loglinear Negative Binomial model, and the resulting estimates for (β, c) and their standard errors are combined using PROC MIANALYZE to get a combined estimate with a corresponding standard error for each parameter:

```
*--- analyze each imputed dataset ---;

PROC GENMOD DATA=_55drop;
  BY _imputation_;
  CLASS usubjid TRTP(REF="Placebo") REGION1 (REF="North America")
NUMPES(REF=">=3") PSAECOL(REF="Negative") AGEGR3(REF="Adult");
  MODEL aval = trtp region1 psaecol numpesagegr3
              / DIST=nb LINK=log OFFSET=log_T COVB WALD TYPE3 NOINT;
  repeated subject=usubjid / type=unstr covb;
  by iteration;
  LSMEANS trtp /exp OM CL;
  ESTIMATE 'brensocatib 10 vs placebo' TRTP 1 0 -1 / EXP E ;
  ESTIMATE 'brensocatib 25 vs placebo' TRTP 0 1 -1 / EXP E ;
  ODS OUTPUT ESTIMATES=_60ests;
RUN;
```

```
*--- combine results with MIANALYZE ---;

PROC MIANALYZE data=_60ests;
  MODELEFFECTS lbetaestimate;
  STDERR stderr;
  by label;
  ODS OUTPUT PARAMETERESTIMATES=_65est;
RUN;
```

Modified procedure for tipping point analysis:

A modified Step 2 is needed to implement the reduced treatment effects under the MNAR scenarios. To reduce differences due to simulation errors it is suggested to use the same underlying set of random numbers for the MAR scenario and for each MNAR scenario as follows:

- Use the same set of simulated parameters (from **Step 1**) generated for the MAR scenario also for all MNAR scenarios.
- Multiply $\psi_2$with the corresponding adjustment factors for each MNAR scenario (i.e., decreased ψ_2 in the placebo arm, increased ψ_2 in the brensocatib arms).

  The SAS-Code with macro variable that describes the adjustment is (The magnitude of the adjustment is defined in Section 8.2.2):

  ```
  PSI2_Adj = PSI2 * &adjust.
  ```

- Simulate the number of PEs Y_2 for Period 2 based on:

  ```
  Y2 = RAND('NEGBINOMIAL', P_STAR_Adj, K_STAR);
  ```

  where p^* has been updated to reflect the adjusted ψ_2.

The above steps will ensure that differences between MAR and MNAR scenarios are mainly due to the systematic differences between the different MNAR adjustments and not just the result of simulation errors.

Secondary Endpoint: Time to first PE – Main analysis

Cumulative first PE incidence rates over the 52-Week treatment period:

```
PROC LIFETEST DATA=<dataIn> METHOD=KM TIMELIST=(12,24,36,52) REDUCEOUT;
   TIME ttpe * cnsr(1);
   STRATA trt;
RUN;
```

Where:

ttpe	time to the first PE event (in weeks)
cnsr	censoring flag (1=censored, 0=event)
trt	participants treatment (brensocatib 25mg, brensocatib 10mg, placebo)

For the incidence rates the survival probability will be subtracted from 1. For the KM estimate at weeks 12, 24, and 36, the survival probability will be displayed.

Covariate-adjusted Cox proportional hazards regression model:

```
PROC PHREG DATA=<dataIn> COVS(AGGREGATE);
  CLASS trtp(REF="Placebo") region1 numpes psaecol agegr3 /
        PARAM=REFERENCE;
  MODEL ttpe * cnsr(1) = trtp region1 numpes psaecol agegr3 /
        TIES=EXACT ALPHA=<0.005, 0.0005> RISKLIMITS;
RUN;
```

Where:

trtp	participants treatment (1=brensocatib 25mg, 2=brensocatib 10mg, 3=placebo)
region1	stratification factor: region1
psaecol	stratification factor: sputum sample being classified as positive or negative for Pseudomonas aeruginosa at screening visit
numpes	stratification factor: number of prior Pes [<3 or ≥3] in the previous 12 months
ttpe	time to the first PE event (in weeks)
agegr3	adult, adolescent

Sorting: data will be sorted by region1, psaecol, numpes, agegr3, ttpe, and usubjid

Secondary Endpoint: Time to first PE – Tipping Point (Sensitivity Analysis)

NOTE: Steps 2 to 5 will be repeated varying delta (δ) for Brensocatib and Placebo. As described in step 3, &_delta_a and &_delta_p will be macro variables set to the delta adjustments for Brensocatib and Placebo respectively. Delta = 1 reflects no delta adjustment.

Step 1: Create a dataset named tte containing 1 row per participant and the following variables

usubjid	participants identifier
trtn	participants treatment (1=brensocatib 25mg, 2=brensocatib 10mg, 3=placebo)
region1	stratification factor: region
psaecol	stratification factor: sputum sample for Pseudomonas aeruginosa at Screening Visit (1=positive or 0=negative)
numpes	Stratification factor: number of prior Pes in the previous 12 months (1= <3, 0= ≥3)
agegr3	age group: adult, adolescent
ttpe	Time to first pulmonary exacerbation event
cnsr	Censoring flag (1=censored, 0=event); NOTE: participants with intercurrent events will be censored.

Step 2: Fit a bayesian piecewise exponential model using the default of 8 intervals – assuming piecewise constant hazards and a gamma prior outputting the survival estimates for each set of covariates into pred1 dataset.

The below estimates the survival function $\hat{S} = (c_i|x_i, \hat{\beta})$ where c_i is the censoring time of participant i, x_i is a vector of participants covariate values observed at or prior to initiation of study treatment, and $\hat{\beta}$ is a vector of model parameters samples from a posterior Bayesian distribution of model parameters estimated from the observed data.

```
PROC SORT DATA=tte OUT=inRisks(KEEP=trtn region1 numpes psaecol  agegr3)
NODUPKEY;
  BY trtn region1  psaecol numpes agegr3;
RUN;

PROC PHREG DATA=tte COVS(AGGREGATE);
  CLASS trtp (REF=Placebo)
        region1 (REF="North America")
        psaecol (ref="Negative")
        numpes (ref=">=3")
        agegr3 (ref="Adult");
  MODEL ttpe * cnsr(1)=trtp region1 psaecol numpes agegr3
                    / TIES=EXACT RISKLIMITS ALPHA=0.05 ;
  BASELINE COVARIATES=inrisks OUT=Pred1 SURVIVAL=_ALL_;
  BAYES SEED=351985287 PIECEWISE=HAZARD (NINTERVAL=8 PRIOR=GAMMA)
    NBI=2000 THINNING=10 NMC=10000;
RUN;
```

<u>Step 3:</u> Merge the survival function estimates for each set of covariates back onto the tte input dataset, following steps b.1 to b.3 below.

(b.1) Compute $p_i = 1 - \hat{S}(c_i|x_i, \hat{\beta})$
(b.2) Draw a uniform random value $u_i \sim \text{uniform}[p_i, 1]$
(b.3) Impute the event time t_i^* as the solution of $u_i = 1 - \hat{S}(t|x_i, \hat{\beta})$. This will ensure that the imputed event time will be greater than the censoring time (and in fact the imputed time will be sampled from the conditional survival $\hat{S}(t|t > c_i, x_i, \hat{\beta})$).

Note that when delta (δ) is not equal to 1 replace in $u_i = 1 - \hat{S}(t|x_i, \hat{\beta})$ in step b.3 with $u_i = 1 - \hat{S}(t|x_i, \hat{\beta})^{\delta}$ (set delta different for each treatment group):

(b.2) will be repeated 100 times creating 100 separate datasets each of which will be used to estimate the event times per participant as follows:

```
*--- merging survival estimate back to original dataset ---;

PROC SQL;
  CREATE TABLE tte2 AS
  SELECT pred1.survival,
        tte.trtn, tte. Region1, tte.psaecol,
        tte.numpes, tte.agegr3, tte.ttpe, tte.usubjid, tte.cnsr
  FROM tte LEFT JOIN pred1
  ON pred1.trtn =tte.trtn AND pred1.region1 =tte.region1 AND
     pred1.psaecol =tte.psaecol AND pred1.numpes=tte.numpes AND
     pred1.agegr3=tte.agegr3
     pred1.ttpe =tte.ttpe;
QUIT;

*--- ensuring survival estimate presents for all rows ---;

DATA tte3 (DROP=survival);
  SET tte2;
  BY trtn region1 psaecol numpes agegr3;
  RETAIN o_surv;
  IF FIRST.numpes THEN o_surv=.;
  IF survival ne . THEN o_surv=survival;
  ELSE IF survival =. THEN survival=o_surv;
RUN;

*--- Compute failure function p=1-survival curve (separate curves for
       each set of covariates) ---;
*--- Draw a uniform random value constrained to be >p and < 1 ---;
*--- &_delta_a and &_delta_p will be macro variables set to the delta
adjustments for Brensocatib and Placebo respectively. The entire set of
code steps 2-5 are repeated separately for each delta tipping point ---;

DATA tte4 (RENAME=ttpe =o_ttpe);
  SET tte3;
```

```
  IF trtn=1 THEN p=1-(o_surv**&_delta_a.); *failure rate – adjusted for
                                           delta for active treatment*;
  ELSE IF trtn=3 THEN p=1-(o_surv**&_delta_p.); *failure rate – adjusted
                                                  for delta for placebo
                                                  treatment*;
  u=RAND('uniform',p,1);  *new failure rate*;
  n_surv=1-u; *new survival rate*;
RUN;

*--- merge u back to the survival function to find the time which
       corresponds to the new survival estimate – which is always >
       censored one ---;
*--- if there isn't a record at exactly n_surv, then we want the latest
       survival estimate prior to that as the survival estimate ---;

PROC SQL;
  CREATE TABLE tte5 as
  SELECT pred1.ttpe, pred1.survival,
        tte4.trtn, tte4.region1, tte.agegr3
        tte4.psaecol, tte4.numpes, tte4.usubjid, tte4.cnsr, tte4.p, tte4.u,
        tte4.n_surv, tte4.o_ttpe, tte4.o_surv
  FROM tte4 LEFT JOIN pred1
  ON pred1.trtn=tte4.trtn AND pred1.region1=tte4.region1 AND
     pred1.psaecol =tte4.psaecol AND pred1.numpes=tte4.numpes AND
     pred1.survival >= tte4.n_surv;
QUIT;

PROC SORT DATA=tte5 (RENAME=(ttpe=pred_ttpe)) OUT=tte6;
  BY trtn region1 psaecol numpes agegr3 usubjid n_surv DESCENDING p_surv;
RUN;

DATA tte7;
  SET tte6;
  BY trtn region1 psaecol numpes agegr3 usubjid n_surv DESCENDING p_surv;
  IF LAST.usubjid THEN OUTPUT;
RUN;

The variable pred_ttpe is the new predicted Time to Pulmonary Exacerbation
event.
```

<u>Step 4:</u> Using the original tte dataset, replace any participants censored prior to Week 52 as identified using ttpe and cnsr, with the pred_ttpe from the above process, updating their censoring flag to be an event. Note: this will create 100 datasets separately for each delta tipping point. Each of the datasets will be analyzed using a cox proportional hazards model outputting the parameter estimate and standard error for the trtn (Active vs Placebo) comparison (for example - into pe1 to pe100).

```
ODS OUTPUT PARAMETERESTIMATES=PE&i.;
PROC PHREG DATA=tte8 COVS(AGGREGATE);
  CLASS trtn (REF="PLACEBO")
        region1
```

```
        psaecol
        numpes
        agegr3;
  MODEL ttpe*cnsr(1)=trt01p region1 psaecol numpes agegr3
                    / TIES=EXACT RISKLIMITS ALPHA=0.05;
RUN;
ODS OUTPUT CLOSE;
```

Step 5: combine the estimates for the 100 datasets into I_PE, and use mianalyze in order to give 1 p-value for the treatment comparison corresponding to each delta value fitted.

```
PROC MIANALYZE DATA= i_PE;
   MODELEFFECTS estimate;
   STDERR stderr;
   ODS OUTPUT PARAMETERESTIMATES = i_output&i.;
RUN;
```

Secondary Endpoint: Status for exacerbation free over the 52-week treatment period

```
PROC LOGISTIC DATA=<dataIn>;
  CLASS trtn(REF='3')
        region1(REF='North America')
        numpes(REF='>=3')
        psaecol(REF='Negative')
        agegr3(REF='Adult');
  MODEL statusn(EVENT='1') = trtp region1 numpes psaecol agegr3 /
    CLODDS=WALD ORPVALUE;
  ODDSRATIO "COMPARISON" trtp / DIFF=ALL CL=WALD ;
  ODS OUTPUT ODDSRATIOSWALD=<dataOut> MODELANOVA=<dataOut>;
RUN;
```

trtp	participants treatment (brensocatib 25mg, brensocatib 10mg, placebo)
region1	stratification factor: North America, Europe, Japan, and the Rest of the World
psaecol	stratification factor: sputum sample being classified as positive or negative for Pseudomonas aeruginosa at screening visit
numpes	stratification factor: number of prior PEs [<3 or ≥3] in the previous 12 months
statusn	status variable with 1=responder and 2=non-responder
agegr3	age group: adult, adolescent

Secondary Endpoint: imputation of missing event times for participants who discontinued early without an exacerbation

Step 1: Create a dataset named tte containing 1 row per participant and the following variables

usubjid	participants identifier
trtp	participants treatment (brensocatib 25mg, brensocatib 10mg, placebo)
region1	stratification factor: North America, Europe, Japan, and the Rest of the World
psaecol	stratification factor: sputum sample being classified as positive or negative for Pseudomonas aeruginosa at screening visit
numpes	stratification factor: number of prior PEs [<3 or ≥3] in the previous 12 months
trtp	participants treatment (brensocatib 25mg, brensocatib 10mg, placebo)
ttpe	Time to first pulmonary exacerbation event
cnsr	Censoring flag (1=censored, 0=event);

Note: Participants who discontinued the study early without a PE will be censored at the time of discontinuation for implementation of Step 3 below.

<u>Step 2:</u> Fit a bayesian piecewise exponential model using the default of 8 intervals – assuming piecewise constant hazards and a gamma prior outputting the survival estimates for each set of covariates into pred1 dataset.

The below estimates the survival function $\hat{S} = (c_i|x_i, \hat{\beta})$ where c_i is the censoring time of participant i, x_i is a vector of participants covariate values observed at or prior to initiation of study treatment, and $\hat{\beta}$ is a vector of model parameters samples from a posterior Bayesian distribution of model parameters estimated from the observed data.

```
PROC SORT DATA=tte OUT=inRisks(KEEP=trtn region1 psaecol numpes agegr3)
NODUPKEY;
  BY trtn region1 psaecol numpes agegr3;
RUN;

PROC PHREG DATA=tte COVS(AGGREGATE);
  CLASS trtp (REF="Placebo") region1(REF="North America")
        numpes (ref=">=3") psaecol (ref="Negative") agegr3 (ref="Adult");
  MODEL ttpe * cnsr(1)=trtn region1 numpes psaecol agegr3
                    / TIES=EXACT RISKLIMITS ALPHA=0.05 ;
  BASELINE COVARIATES=inrisks OUT=Pred1 SURVIVAL=_ALL_;
  BAYES SEED=351985287 PIECEWISE=HAZARD (NINTERVAL=8 PRIOR=GAMMA)
    NBI=2000 THINNING=10 NMC=10000;
RUN;
```

<u>Step 3:</u> Merge the survival function estimates for each set of covariates back onto the tte input dataset, following steps b.1 to b.3 below.

(b.1) Compute $p_i = 1 - \hat{S}(c_i|x_i, \hat{\beta})$
(b.2) Draw a uniform random value $u_i \sim \text{uniform}[p_i, 1]$
(b.3) Impute the event time t_i^* as the solution of $u_i = 1 - \hat{S}(t|x_i, \hat{\beta})$. This will ensure that the imputed event time will be greater than the censoring time (and in fact the imputed time will be sampled from the conditional survival $\hat{S}(t|t > c_i, x_i, \hat{\beta})$).

(b.2) will be repeated 100 times creating 100 separate datasets each of which will be used to estimate the event times per participant as follows:

```
*--- merging survival estimate back to original dataset ---;

PROC SQL;
  CREATE TABLE tte2 AS
  SELECT pred1.survival,
        tte.trtn, tte. Region1, tte.psaecol,
        tte.numpes, tte.agegr3, tte.ttpe, tte.usubjid, tte.cnsr
  FROM tte LEFT JOIN pred1
  ON pred1.trtn =tte.trtn AND pred1.region1 =tte.region1 AND
     pred1.psaecol =tte.psaecol AND pred1.numpes=tte.numpes AND
     pred1.agegr3=tte.agegr3 AND
     pred1.ttpe =tte.ttpe;
QUIT;
```

```
*--- ensuring survival estimate presents for all rows ---;

DATA tte3 (DROP=survival);
  SET tte2;
  BY trtn region1 psaecol numpes agegr3;
  RETAIN o_surv;
  IF FIRST.numpes THEN o_surv=.;
  IF survival ne . THEN o_surv=survival;
  ELSE IF survival =. THEN survival=o_surv;
RUN;

*--- Compute failure function p=1-survival curve (separate curves for
       each set of covariates) ---;
*--- Draw a uniform random value constrained to be >p and < 1 ---;
*--- use 100 different seeds to ensure reproducibility ---;

DATA createSeed;
  CALL STREAMINIT(351985287);
  DO i=1 TO 100;
    _seed=1000 + INT(RAND("UNIFORM")*10000000);
    OUTPUT;
  END;
RUN;


DATA tte4 (RENAME=ttpe =o_ttpe);
  SET tte3;
  call streaminit(<SEED from above dataset>);
  p=1-(o_surv);
  u=RAND('uniform',p,1);  *new failure rate*;
  n_surv=1-u; *new survival rate*;
RUN;

*--sort by descending n_surv and keep only rows with subjid present ---;
proc sort data=tte4 (keep=usubjid n_surv trtn region1 psaecol numpes
agegr3 where=(subjid ne ""));
by trtn region1 psaecol numpes agegr3 descending n_surv subjid;
run;

*--- merge u back to the survival function to find the time which
       corresponds to the new survival estimate - which is always >
       censored one ---;
*--- if there isn't a record at exactly n_surv, then we want the latest
       survival estimate prior to that as the survival estimate ---;

PROC SQL;
  CREATE TABLE tte5 as
  SELECT pred1.ttpe, pred1.survival,
        tte4.trtn, tte4.region1, tte.agegr3
        tte4.psaecol, tte4.numpes, tte4.usubjid, tte4.cnsr, tte4.p, tte4.u,
        tte4.n_surv, tte4.o_ttpe, tte4.o_surv
```

```
  FROM tte4 LEFT JOIN pred1
  ON pred1.trtn=tte4.trtn AND pred1.region1=tte4.region1 AND
     pred1.psaecol =tte4.psaecol AND pred1.numpes=tte4.numpes AND
     pred1.survival >= tte4.n_surv;
QUIT;

PROC SORT DATA=tte5 (RENAME=(ttpe=pred_ttpe)) OUT=tte6;
  BY trtn region1 psaecol numpes agegr3 usubjid n_surv DESCENDING o_surv;
RUN;

DATA tte7;
  SET tte6;
  BY trtn region1 psaecol numpes agegr3 usubjid n_surv DESCENDING o_surv;
  IF LAST.usubjid THEN OUTPUT;
RUN;
```

The variable pred_ttpe is the new predicted Time to Pulmonary Exacerbation event.

<u>Step 4:</u> Using the original tte dataset, replace any participants censored prior to Week 52 as identified using ttpe and cnsr, with the pred_ttpe from the above process, updating their censoring flag to be an event. Participants with an imputed event which is less than Day 365 will be considered non-responders. Participants with imputed event which is >= Day 365 will be considered Responders (as we predict they would not have have a PE prior to Week 52 even if they remained on the study). Note: this will create 100 datasets. Each of the datasets will be analyzed using a logistic regression model outputting the parameter estimate and standard error for the trtn (Active vs Placebo) comparison (for example - into pe1 to pe100).

Skeleton code for this part may be based on the following.

```
PROC LOGISTIC DATA=tte8;
  BY _imputation_;
  CLASS trtp (ref="Placebo") REGION1(ref="North America")
        numpes (ref=">=3") psaecol (ref="Negative") agegr3 (ref="Adult");
  MODEL statusn = trtn region1 numpes psaecol agegr3/CLODDS=WALD ORPVALUE;
  ODS OUTPUT PARAMETERESTIMATES=pes COVB=lgscovb;
RUN;
```

Step 5: combine the estimates for the 100 datasets into I_PE, and use mianalyze in order to give 1 p-value for the treatment comparison corresponding to each delta value fitted.

Skeleton code for this part may be based on the following.

```
PROC MIANALYZE PARMS(CLASSVAR=CLASSVAL)=PES;
   CLASS trtp region1 numpes psaecol agegr3
   MODELEFFECTS trtp region1 numpes psaecol agegr3;
   ODS OUTPUT PARAMETERESTIMATES=pes2;
RUN;
```

Secondary Endpoint: Change from baseline in Post-bronchodilator FEV1 at Week 52 – MAIN ANALYSIS

The SAS-Code is the same as defined below in Step 5, except that the main analysis will have no BY-Statement.

Please make sure that records for missing post-randomization visits of participants included in the analysis are artificially created. In the added records the value of the response variable will be missing, but the full information on covariates must be included. This is to create a full correlation structure per participant among (expected) study visits. Refer to below example for visualization with visit 3 to 6 expected:

Dataset as per recorded data: Participants 2 and 3 with missing visits

Participant	Treatment	Covariate	Baseline	Visit	Change from baseline
1	Brensocatib 10mg QD	X	X	3	X
1	Brensocatib 10mg QD	X	X	4	X
1	Brensocatib 10mg QD	X	X	5	X
1	Brensocatib 10mg QD	X	X	6	X
2	Placebo	X	X	3	X
3	Brensocatib 25mg QD	X	X	3	X
3	Brensocatib 25mg QD	X	X	6	X

Dataset with added records for missing visits (italic) but full information on covariates:

Participant	Treatment	Covariate	Baseline	Visit	Change from baseline
1	Brensocatib 10mg QD	X	X	3	X
1	Brensocatib 10mg QD	X	X	4	X
1	Brensocatib 10mg QD	X	X	5	X
1	Brensocatib 10mg QD	X	X	6	X
2	Placebo	X	X	3	X
2	Placebo	X	X	4	.
2	Placebo	X	X	5	.
2	Placebo	X	X	6	.
3	Brensocatib 25mg QD	X	X	3	X
3	Brensocatib 25mg QD	X	X	4	.
3	Brensocatib 25mg QD	X	X	5	.
3	Brensocatib 25mg QD	X	X	6	X

Secondary Endpoint: Change from baseline in Post-bronchodilator FEV1 at Week 52 – Tipping Point (Sensitivity Analysis)

NOTE: Steps 2 to 6 will be repeated varying delta (δ) for brensocatib and placebo. As described in step 3, `&i_act10.` and `&i_pbo10`, `&i_act25.` and `&i_pbo25..` will be macro variables set to the delta adjustments for brensocatib and placebo respectively, for the 10mg vs Placebo comparison and the 25mg vs Placebo comparison.

Step 1: Create a dataset i_input1 containing 1 row per participant and the following variables

usubjid	participants identifier
trtn	participants treatment (1=active 25mg, 2=active 10mg, 3=placebo)
region1	stratification factor: region (set of 3 dummy (0/1) variables to represent Europe, ROW and Japan, With North America as reference category)
psaecol	stratification factor: sputum sample for Pseudomonas aeruginosa at Screening Visit (1=positive or 0=negative as the reference)
numpes	Stratification factor: number of prior PEs in the previous 12 months (1= <3, 0= ≥3 as the reference)
agegr3	age group: 0=adult, 1=adolescent (with Adult as reference category)
Baseline	Baseline post-bronchodilator FEV_1
Wk16	Week 16 post-brochodilator FEV_1
wk28	Week 28 post-brochodilator FEV_1
wk40	Week 40 post-brochodilator FEV_1
wk52	Week 52 post-brochodilator FEV_1

Step 2: Impute the intermittent (non-monotone) missing data

```
NOTE: Binary (0/1) variables will be used for the factors of region,
pseudon numpes agegr3 to represent all levels (ie. 3 region binary
variables representing Europe, ROW and Japan, with North America as the
reference)
PROC MI DATA=i_input1 SEED=123456 NIMPUTE=100 OUT=i_mono;
  MCMC IMPUTE=MONOTONE NBITER=200 CHAIN=MULTIPLE PRIOR=JEFFREYS;
  VAR Europe ROW Japan pseudon numpes agegr3 baseline wk16 wk28 wk40 wk52;
RUN;
```

Step 3: Impute the monotone missing data using an adjustment for the delta tipping point adjustment.

Note; as separate deltas will be used for each of the 10mg and 25mg treatments, the model will be run twice using the deltas respective to each Brensocatib treatment group (act10/pbo10 or act25/pbo25).

```
PROC MI DATA=i_mono SEED=123456  NIMPUTE=1 OUT=i_nomiss NOPRINT;
  BY _IMPUTATION_;
  CLASS trtn;
  VAR trtn Europe ROW Japan pseudon numpes agegr3 baseline wk16 wk40 wk52;
  MONOTONE REG(baseline=trtn Europe ROW Japan pseudon numpes/DETAILS);
  MONOTONE REG(wk16=trtn Europe ROW Japan pseudon numpes baseline/DETAILS);
```

```
  MONOTONE REG(wk28=trtn Europe ROW Japan pseudon numpes baseline
wk16/DETAILS);
  MONOTONE REG(wk40=trtn Europe ROW Japan pseudon numpes baseline wk16
wk28/DETAILS);
  MONOTONE REG(wk52=trtn Europe ROW Japan pseudon numpes baseline wk16 wk28
wk40/ DETAILS);

  MNAR ADJUST(baseline / SHIFT=&i_act10. ADJUSTOBS=(trtn="1" "2"));
  MNAR ADJUST(wk16     / SHIFT=&i_act10. ADJUSTOBS=(trtn="1" "2"));
  MNAR ADJUST(wk28     / SHIFT=&i_act10. ADJUSTOBS=(trtn="1" "2"));
  MNAR ADJUST(wk40     / SHIFT=&i_act10. ADJUSTOBS=(trtn="1" "2"));
  MNAR ADJUST(wk52     / SHIFT=&i_act10. ADJUSTOBS=(trtn="1" "2"));

  MNAR ADJUST(baseline / SHIFT=&i_pbo10. ADJUSTOBS=(trtn="3"));
  MNAR ADJUST(wk16     / SHIFT=&i_pbo10. ADJUSTOBS=(trtn="3"));
  MNAR ADJUST(wk28     / SHIFT=&i_pbo10. ADJUSTOBS=(trtn="3"));
  MNAR ADJUST(wk40     / SHIFT=&i_pbo10. ADJUSTOBS=(trtn="3"));
  MNAR ADJUST(wk52     / SHIFT=&i_pbo10. ADJUSTOBS=(trtn="3"));
RUN;
```

Notes:

- `_IMPUTATION_` variable represents an ID variable 1 to 100 representing the 100 imputed datasets from the step above.
- The macro variable `&i_act10 and &i_act25.` will contain the delta shift for actual treatment (25mg or 10mg) and `&i_pbo10 and &i_pbo25.` will contain the delta shift for the placebo treatment. The range of delta will be –3*X to +3*X by 0.01 litre increments, where X=observed treatment effect difference in litres (active – placebo) at Week 52 for the main model analysis. In order to obtain a range of delta symmetrical around 0, X will be rounded to 2 decimal places prior to multiplication. For example, if the treatment difference (25mg – placebo) in FEV1 at Week 52 = 0.01 litres, the following table of deltas will be used in order to calculate the p-values corresponding to the grey shaded boxes. A delta of 0ml corresponds to no delta increment/decrement.

Table 20: Secondary Endpoint - Change from Baseline (FEV1): Tipping Point Analysis - Delta Increment / Decrement

			Brensocatib 25 mg – Placebo = 10 ml (0.01 litres) = x						
			Active Delta						
			-30 ml	-20 ml	-10 ml	0 ml	+10 ml	+20 ml	+30 ml
			-3*x	-2*x	-1*x	0	+1*x	+2*x	+3*x
Placebo Delta	-30 ml	-3*x							
	-20 ml	-2*x							
	-10 ml	-1*x							
	0 ml	0*x							
	+10 ml	+1*x							
	+20 ml	+2*x							
	+30 ml	+3*x							

Step 4: Transform the i_nomiss dataset to have 1 row per participant per visit and the following variables (i_mod1)

imputation	Imputation number from 1 to xx representing the xx imputed datasets in the steps above
usubjid	participants identifier
trtn	participants treatment (1=active 25mg, 2=active 10mg, 3=placebo)
Region1	stratification factor: region1 (With North America as reference category)
psaecol	stratification factor: sputum sample for Pseudomonas aeruginosa at Screening Visit (positive or negative as the reference)
numpes	Stratification factor: number of prior PEs in the previous 12 months (<3, ≥3 as the reference)
agegr3	age group: adult, adolescent (With Adult as the reference)
baseline	Baseline post-bronchodilator FEV1
aval	Post-bronchodilator FEV1 at AVISITN as per the xx imputed datasets
chg	Change from baseline for post-bronchodilator FEV1 at AVISITN (calculated as AVAL-Baseline)
avisit	Visit identifier corresponding to the change from baseline result (1=Wk16, 2=Wk28, 3=Wk40, 4=Wk52)

Step 5: Fit a MMRM, storing output for each of the 100 imputed datasets corresponding to each fitted delta combination.

```
PROC MIXED DATA=i_mod1 METHOD=REML ORDER=DATA EMPIRICAL;
  BY _imputation_;
  CLASS usubjid trt01pn(ref="3") visit region1(ref="North America")
numpes(ref=">=3") psaecol(ref="Negative") agegr3(ref="Adult");
  MODEL  chg = trt01pn avisit trt01pn*avisit region1 numpes psaecol agegr3
baseline / SOLUTION;
  REPEATED visit / SUBJECT=usubjid TYPE=CS RCORR;
  LSMESTIMATE trt01pn
    'Brensocatib 10mg QD vs Placebo: Overall'  1 0 -1,
    'Brensocatib 25mg QD vs Placebo: Overall'  0 1 -1 / CL OM ALPHA=0.05;
  LSMESTIMATE trt01pn*visit
    'Brensocatib 10mg QD vs Placebo: Week 16'  1 0 0 0  0 0 0 0  -1 0 0 0,
    'Brensocatib 10mg QD vs Placebo: Week 28'  0 1 0 0  0 0 0 0   0 -1 0 0,
    'Brensocatib 10mg QD vs Placebo: Week 40'  0 0 1 0  0 0 0 0   0 0 -1 0,
    'Brensocatib 10mg QD vs Placebo: Week 52'  0 0 0 1  0 0 0 0   0 0 0 -1,

    'Brensocatib 25mg QD vs Placebo: Week 16'  0 0 0 0  1 0 0 0  -1 0 0  0,
    'Brensocatib 25mg QD vs Placebo: Week 28'  0 0 0 0  0 1 0 0   0 -1 0 0,
    'Brensocatib 25mg QD vs Placebo: Week 40'  0 0 0 0  0 0 1 0   0 0 -1 0,
    'Brensocatib 25mg QD vs Placebo: Week 52'  0 0 0 0  0 0 0 1   0 0 0 -1
/ CL OM ALPHA=0.05;
  ODS OUTPUT  LSMEANS       =_10lsm
              LSMESTIMATES  =_11est;
RUN;
```

NOTE: the 11est dataset will be used to store the mean difference (estimate) and standard error (stderr) for the comparison between active and placebo at Week 52 for each delta adjustment dataset for the 100 imputed datasets.

Step 6: combine the estimates using mianalyze

The code below will be run for each delta adjustment dataset combining the 100 imputed datasets.

```
PROC MIANALYZE DATA=11est;
  MODELEFFECTS estimate;
  STDERR stderr;
  BY label;
  ODS OUTPUT PARAMETERESTIMATES=i_output;
RUN;
```

Secondary Endpoint: Change from Baseline in QoL-B Respiratory Symptoms Domain Score at Week 52

MAIN ANALYSIS

```
PROC MIXED DATA=<dataIn> EMPIRICAL;
  CLASS usubjid trtpn(REF='3') region1 numpes psaecol atptn;
  MODEL chg=trtpn region1 numpes pasecol baseline
             atptn trtpn* atptn;
  REPEATED atptn / SUBJECT=usubjid TYPE=CS RCORR;
  LSMEANS trtpn*atptn / OM CL DIFF=ALL ALPHA=<>;
  ODS OUTPUT DIFFS=<dataOut>;
RUN;
```

usubjid	participants identifier
trtpn	participants treatment (brensocatib 10mg, brensocatib 10mg, placebo)
region1	stratification factor: North America, Europe, Japan, and the Rest of the World
psaecol	stratification factor: sputum sample being classified as positive or negative for Pseudomonas aeruginosa at screening visit
numpes	stratification factor: number of prior PEs [<3 or ≥3] in the previous 12 months
baseline	Baseline post-bronchodilator FEV1
chg	Change from baseline for post-bronchodilator FEV1 at AVISITN (calculated as AVAL-Baseline)
atptn	Visit identifier corresponding to the change from baseline result; refer to the mapping of visits in Section 6.7.5.2

Secondary Endpoint: Change from baseline in QoL-B Respiratory Symptoms Domain Score at Week 52 – Tipping Point (Sensitivity Analysis)

The same analysis as described for Change from Baseline in Post-bronchodilator FEV1 (L) at Week 52 will be applied.

The range of delta will be determined in the same way using –3*X to +3*X by a suitable increment, where X=observed treatment effect difference (active – placebo) at Week 52 for the main model analysis. The increment will be selected in order to give suitable detail regarding the tipping point. In order to obtain a range of delta symmetrical around 0, X will be rounded to the same decimal places as the incremental parameter precision prior to multiplication.

Exploratory assessments

A graph consisting of the change from baseline in the QoL-B Respiratory Symptoms Domain to Week 52 (CHG) on the horizontal axis and the cumulative percent of participants experiencing up to that change on the vertical axis will be produced to represent the eCDF.

Participants with missing data will be considered non-responders. See Section 6.7.5.4 and 6.7.5.5.

Mean Cumulative Function

The mean cumulative function will be obtained by PHREG procedure in SAS. Input will be the analysis dataset ADCE. Before calling PHREG, for each participant the time between Pes (event-free time) and the time from last PE until Week 52 needs to be added. This artificial entry will be censored.

An example of the data structure is given below:

Participant	ASTDY	AENDY	CENS	In ADCE	Artificial
1	45	90	0	1	
1	90	122	1		1
1	123	130	0	1	
1	131	319	1		1
1	320	329	0	1	
1	330	364	1		1

```
DATA in1;
  trtpn=1; OUTPUT;
  trtpn=2; OUTPUT;
  trtpn=3; OUTPUT;
RUN;

PROC PHREG DATA=_06cens COVS(AGGREGATE) COVM;
  MODEL (astdy,aendy) * cens(1) = trtpn;
  BASELINE COVARIATES=IN1 OUT=_10phreg CMF=_ALL_ / NOMEAN;
  ID subjid;
RUN;
```

Random coefficients regression model for Rate of Change in Prebronchodilator and Postbronchodilator FEV_1 Over the 52-Week Treatment Period

```
PROC MIXED DATA=… METHOD=REML;
  CLASS trtp subject;
  MODEL FEV1=trtp time trtp*time / S OUTP=prediction DDFM=KR;
  RANDOM intercept time / TYPE=UN SUB=SUBJECT;
  ESTIMATE "Regr. coeff. Brensocatib 10mg QD"   time 1 time*trtp 1 0 0/CL;
  ESTIMATE "Regr. coeff. Brensocatib 25mg QD"   time 1 time*trtp 0 1 0/CL;
  ESTIMATE "Regr. coeff. Placebo QD"            time 1 time*trtp 0 0 1/CL;
RUN;
```

Estimate of risk difference and exact 95% confidence interval for AESI

```
PROC FREQ DATA=_01get ORDER=DATA;
  TABLE trta * <hypfl,pgfl,infsfl,pneufl> / RISKDIFF(CL=EXACT COLUMN=x);
  EXACT RISKDIFF(METHOD=SCORE);
RUN;

Please note that variables <hypfl,pgfl,infsfl,pneufl> are binary (Y/N) with
<hypfl,pgfl,infsfl,pneufl>=Y for specific type of AESI, otherwise N.
```

APPENDIX J. TECHNICAL DETAILS FOR PROPOSED MIXTURE-BASED GATEKEEPING PROCEDURE

Adjusted p values for testing individual null hypotheses

The appendix presents the multiplicity-adjusted p-values for the mixture-based gatekeeping procedure. The following notation will be used:

- The raw p-values are denoted by p_1 through p_{12}.
- The adjusted p-values are denoted by $\tilde{p}_1$ through $\tilde{p}_{12}$.

The following function will be used to define the multiplicity-adjusted p-values for the individual null hypotheses:

$f(p,q) = 2\min(p/(1+\gamma_1), q/(1-\gamma_1))$, where γ_1 is the truncation parameter of Family 1.

The adjusted p-values are given by:

$$\tilde{p}_1 = \max\left(p_1, \min\left(2p_{(1)}, p_{(2)}\right), f(p_1,p_4), f(p_1,p_6), f(p_1,p_8), f(p_1,p_{10}), f(p_1,p_{12})\right),$$

$$\tilde{p}_2 = \max\left(p_2, \min\left(2p_{(1)}, p_{(2)}\right), f(p_2,p_3), f(p_2,p_5), f(p_2,p_7), f(p_2,p_9), f(p_2,p_{11})\right),$$

$$\tilde{p}_3 = \max\begin{pmatrix}\tilde{p}_1, p_3, f(p_2,p_3), 2\min(p_3,p_4), 2\min(p_3,p_6),\\ 2\min(p_3,p_8), 2\min(p_3,p_{10}), 2\min(p_3,p_{12})\end{pmatrix},$$

$$\tilde{p}_4 = \max\begin{pmatrix}\tilde{p}_2, p_4, f(p_1,p_4), 2\min(p_4,p_3), 2\min(p_4,p_5),\\ 2\min(p_4,p_7), 2\min(p_4,p_9), 2\min(p_4,p_{11})\end{pmatrix},$$

$$\tilde{p}_5 = \max\begin{pmatrix}\tilde{p}_3, p_5, f(p_2,p_5), 2\min(p_5,p_4), 2\min(p_5,p_6),\\ 2\min(p_5,p_8), 2\min(p_5,p_{10}), 2\min(p_5,p_{12})\end{pmatrix},$$

$$\tilde{p}_6 = \max\begin{pmatrix}\tilde{p}_4, p_6, f(p_1,p_6), 2\min(p_3,p_6), 2\min(p_5,p_6),\\ 2\min(p_6,p_7), 2\min(p_6,p_9), 2\min(p_6,p_{11})\end{pmatrix},$$

$$\tilde{p}_7 = \max\begin{pmatrix}\tilde{p}_5, p_7, f(p_2,p_7), 2\min(p_7,p_4), 2\min(p_7,p_6),\\ 2\min(p_7,p_8), 2\min(p_7,p_{10}), 2\min(p_7,p_{12})\end{pmatrix},$$

$$\tilde{p}_8 = \max\begin{pmatrix}\tilde{p}_6, p_8, f(p_1,p_8), 2\min(p_8,p_3), 2\min(p_8,p_5),\\ 2\min(p_8,p_7), 2\min(p_8,p_9), 2\min(p_8,p_{11})\end{pmatrix},$$

$$\tilde{p}_9 = \max\begin{pmatrix}\tilde{p}_7, p_9, f(p_2,p_9), 2\min(p_9,p_4), 2\min(p_9,p_6),\\ 2\min(p_9,p_8), 2\min(p_9,p_{10}), 2\min(p_9,p_{12})\end{pmatrix},$$

$$\tilde{p}_{10} = \max\begin{pmatrix}\tilde{p}_8, p_{10}, f(p_1,p_{10}), 2\min(p_{10},p_3), 2\min(p_{10},p_5), 2\min(p_{10},p_7),\\ 2\min(p_{10},p_9), 2\min(p_{10},p_{11})\end{pmatrix},$$

$$\tilde{p}_{11} = \max\begin{pmatrix}\tilde{p}_9, p_{11}, f(p_2,p_{11}), 2\min(p_{11},p_4), 2\min(p_{11},p_6), 2\min(p_{11},p_8),\\ 2\min(p_{11},p_{10}), \min\left(2p_{(11)}, p_{(12)}\right)\end{pmatrix},$$

$$\tilde{p}_{12} = \max\begin{pmatrix}\tilde{p}_{10}, p_{12}, f(p_1,p_{12}), 2\min(p_{12},p_3), 2\min(p_{12},p_5), 2\min(p_{12},p_7),\\ 2\min(p_{12},p_9), \min\left(2p_{(11)}, p_{(12)}\right)\end{pmatrix}.$$

APPENDIX K. DICTIONARY CODES

WHO DRUG DICTIONARY CODES TO IDENTIFY CHRONIC ANTIBIOTICS USE

Identification of medications will be done using the following criteria:

‘ATC2 = 'J01' (ANTIBACTERIALS FOR SYSTEMIC USE) and Route not ‘Intravaginal’, ‘Ophthalmic’,’ Periodontal’, or ‘Vaginal’’.

MEDDRA CODES TO IDENTIFY HISTORY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN AE AND MEDICAL HISTORY DOMAIN THROUGH COMPARISON OF DATES

MedDRA codes – PREFERRED TERM
BRONCHIAL OBSTRUCTION
BRONCHITIS: CONDITIONAL ON PARTICIPANTS WITH AN AGE >=18 YEARS ONLY
BRONCHITIS CHRONIC
CHRONIC BRONCHITIS
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
EMPHYSEMA
OBSTRUCTIVE AIRWAYS DISORDER
PULMONARY EMPHYSEMA

MEDDRA CODES TO IDENTIFY HISTORY OF ASTHMA IN AE AND MEDICAL HISTORY DOMAIN THROUGH COMPARISON OF DATES

MedDRA codes – PREFERRED TERM
ASTHMA
ASTHMA LATE ONSET

WHO DRUG DICTIONARY ATC CODES TO IDENTIFY INHALED STEROID

Get the Inhaled route from CM (cmroute_std = **110)** and then use the ATC4 codes and Preferred Terms as described below:

cmtrt_atc4_code in ('R03BA','R03AL')
OR
cmtrt_atc4_code = 'R03AK' and
cmtrt_product contains he following:
'FLUTICASONE' or
'BECLOMETASONE' or
'BUDESONIDE' or
'MOMETASONE' or
'CICLESONIDE' or
'FLUNISOLIDE' or
'BECLOMETHASONE' or
'DEXAMETHASONE' or
'TIXOCORTOL'

MEDDRA CODES TO IDENTIFY COVID-19 ADVERSE EVENTS

MedDRA codes – PREFERRED TERM
COVID-19
SARS-COV-2 TEST POSITIVE
CORONAVIRUS INFECTION
COVID-19 PNEUMONIA

These terms code to SOC = Infections and infestations or Investigations.

APPENDIX L. BRONCHIECTASIS SEVERITY INDEX

The calculation of the BSI is included on the eCRF "*Bronchiectasis Severity Index*", based on the severity criteria reported on the same form. It was decided to re-calculate the BSI by replacing the below severity criteria of the form:

- FEV1 (%Predicted) from pulmonary function test form at Baseline / Day 1, post-bronchodilator; only assessments selected as indicated in Section 6.7.3
- Exacerbation frequency in last 12 months from randomization form
- Colonization status from randomization form

The calculation will be done according to Chalmers et. al (2014) as shown in below table. The source for severity criteria "Age (Years)", "BMI (kg/m²)", "Hospital Admissions in the Past 2 Years", "MRC Dyspnea Score", and "Radiological Severity" will be the eCRF.

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 in the Past 2 Years	No	-	-	-	-	Yes	-
Exacerbation Frequency in Last 12 Months	0 to 2	-	3 or More	-	-	-	-
MRC Dyspnea Score	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 JD et al, 2014).
BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, MRC = Medical Research Council; *Pa* = *Pseudomonas aeruginosa*.

To note: The colonization status will be coded as

- 0 Point for Pseudomonas colonization=No
- 3 Points for Pseudomonas colonization=Yes

This study will have no assignment of "1 Point" for colonization status. Chronic colonization will be considered as "Pa Colonization".

APPENDIX M. RULES FOR DIFFERENTIATING CHRONIC ANTIBIOTICS USE

Discontinuation from standard of care:

1. Identification of therapies:
To identify participants discontinuing from standard of care, the definition of standard of care is important. Participants will be considered being on standard of care is equal to being on a chronic course of antibiotics without any changes in dose nor administration route at baseline. Therapies of interest are those antibiotics who fit into one of the dictionary codes defined in Appendix K. Antibiotic therapies administered to treat a PE are excluded.

2. Combining therapies: this only applies to therapies with multiple records of the exact same CMDECOD name (the coded therapy name):
Any exact same therapies, ignoring a different dose or frequency, will be combined if intake was reported within 7 days, or if records are overlapping.

Example 01:
- Antibiotics A: start date=15Jun2022, end date=30Sep2022
- Antibiotics A: start date=02Oct2022, end date=07Mar2023
- In those cases, the start date will be determined as 15Jun2022. The end date will be set to 07Mar2023.

Example 02:
- Antibiotics B: start date=15Jun2022, end date=30Sep2022
- Antibiotics B: start date=22Sep2022, end date=ongoing
- In those cases, the start date will be determined as 15Jun2022. The end date will be imputed as defined in Section 6.7.1 for PEs ongoing at EOS or the date of data cut-off for data tabulations during study conduct, e.g., dry-runs.

If exact same therapies are more than 7 days apart (>7), the therapies will be considered as two different therapies.

3. Mark therapies who were stable at baseline:
Any antibiotic therapies started prior to the first administration of IP and who were present at day 1 (baseline), including those ongoing at baseline, and who have a minimum duration of 28 days will be considered as standard of care.

4. Identify standard of care marked therapies who stopped during study conduct.
Any standard of care therapies present at baseline but stopped during study conduct will be identified through comparison of the therapy stop date against date of last IP administration. Please refer to Section 6.4.2 for determination of date of last IP administration.