16.1.9 Documentation of Statistical Methods

The documents listed below are provided in this section.

Statistical Analysis Plan (Study Z7224L01) dated 08-April-2021

Statistical Analysis Plan (Study Z7224L01) Addendum 1 dated 22-July-2021

Statistical Analyses (Study Z7224L01) Note to File dated 09-March-2021

Sponsor:	Zambon S.p.A.	Protocol Number:	Z7224L01

ZAMBON S.p.A

STATISTICAL ANALYSIS PLAN

Protocol: Z7224L01

EudraCT Number 2015-002743-33

Treatment: Inhaled Colistimethate Sodium

A DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTRE, CLINICAL TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF 12 MONTHS OF THERAPY WITH INHALED COLISTIMETHATE SODIUM IN THE TREATMENT OF SUBJECTS WITH NON-CYSTIC FIBROSIS BRONCHIECTASIS CHRONICALLY INFECTED WITH PSEUDOMONAS AERUGINOSA (P. AERUGINOSA)

Author(s):	PPD
Document Status:	Version 2 Final
Version Dates:	08 Apr 2021
Pages:	118

APPROVAL PAGE

Protocol Title: A double-blind, placebo-controlled, multi-centre, clinical trial to investigate the efficacy and safety of 12 months of therapy with inhaled colistimethate sodium in the treatment of subjects with non-cystic fibrosis bronchiectasis chronically infected with *Pseudomonas aeruginosa* (*P. aeruginosa*)

Protocol Name: Promis I

Protocol Code: Z7224L01

Protocol Version and Date: Version 7.0; 22 Oct 2019

EudraCT number: 2015-002743-33

Authors:	PPD
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Contents

Abbreviations

[redacted]	[redacted]
ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CA	Competent Authority
CF	Cystic Fibrosis
CFU	Colony Forming Units
CI	Confidence Interval
CRO	Contract Research Organisation
CS	Clinically Significant
CT	Computerised Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	Data [redacted]
EC	Ethics Committee
eCRF	electronic Case Report Form
eCOA	electronic Clinical Outcome Assessment
ED	Exposure Day
FEV_1	Forced Expiratory Volume in one second
FOE	Frequency of Exacerbations
FVC	Forced Vital Capacity
GLI	Global Lung Function Initiative
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention-To-Treat
IWRS	Interactive Web Response System
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intention-To-Treat (Full Analysis Set)
MIU	Million International Unit
NCFB	Non-CF-Bronchiectasis
NCS	Non Clinically Significant
P. aeruginosa	*Pseudomonas aeruginosa*
PP	Per-Protocol
PT	Preferred Term
PWP	Prentice, Williams and Peterson
[redacted]	[redacted]
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
CCI	[redacted]
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organisation
WHO-DD	WHO Drug Dictionary

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Zambon, Protocol No. Z7224L01: A double-blind, placebo-controlled, multi-centre, clinical trial to investigate the efficacy and safety of 12 months of therapy with inhaled colistimethate sodium in the treatment of subjects with non-cystic fibrosis bronchiectasis chronically infected with *Pseudomonas aeruginosa (P. aeruginosa)*

This analysis plan is based on the final protocol Version 7.0 dated 22Oct2019.

The SAP provides the description of the analysis for the final analyses. Any deviations from the SAP which occur after breaking the blind will be documented and justified in the final clinical trial report (CTR) and deviations will be clearly marked as 'post hoc' analysis.

2 Study Objectives

The primary objective of the trial is to investigate the effect of the use of inhaled colistimethate sodium, administered twice daily via the [redacted] for 12 months, compared to placebo in subjects with non-cystic fibrosis bronchiectasis (NCFB) chronically infected with *P. aeruginosa* on the annualized frequency of pulmonary exacerbations.

2.1 Primary Endpoint

The primary endpoint of this trial is the mean annual NCFB pulmonary exacerbation rate.

A pulmonary exacerbation is defined as the presence concurrently of at least 3 of the following 8 symptoms/signs for at least 24 hours:

- increased cough;
- increased sputum volume and/or consistency;
- increased sputum purulence;
- new or increased haemoptysis;
- increased wheezing;
- increased dyspnoea;
- increased fatigue/malaise;
- episodes of fever (temperature ≥38°C);

And it is clinically determined that the subject requires and is prescribed systemic antibiotic therapy.

The start date of a protocol-defined pulmonary exacerbation will be taken as the first day that at least 3 of the pre-defined 8 symptoms/signs occurred concurrently for at least 24 hours, as determined by the Investigator, as documented by the start date of the corresponding AE in the eCRF AE form.

Resolution of a pulmonary exacerbation is defined as the date of completion of the required course(s) of systemic antibiotic treatment and/or the Investigator's judgement that the NCFB pulmonary exacerbation has resolved, as documented by the end date provided for the corresponding AE in the eCRF AE form, whichever is the later of the two dates. The exacerbation end date will be reported at the next scheduled visit or by phone. A new pulmonary exacerbation is only considered to occur if there are at least 14 days between the end of the course of systemic antibiotics and the onset of new qualifying symptoms.

The treatment of pulmonary exacerbations will follow current treatment regimens used at the respective participating investigational site.

A supportive analysis will be conducted using an alternative definition of NCFB pulmonary exacerbation. The re-classification of exacerbations will be done in a blinded fashion (before database lock). Alternative definition of pulmonary exacerbation: deterioration in three or more of the following key symptoms for at least 48 hours:

- Cough;
- Sputum volume and/or consistency;
- Sputum purulence;
- Breathlessness and/or exercise tolerance (dyspnoea);
- Fatigue and/or malaise;
- Haemoptysis;

And a physician determines a change in bronchiectasis treatment is required when other potential causes of clinical deterioration have been discounted.

2.2 Secondary Endpoints

The secondary endpoints of this trial are:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.3 Safety Endpoints

The safety endpoints of this trial are:

- incidence of treatment emergent adverse events (TEAEs);
- absolute changes in percent-predicted forced expiratory volume in 1 second (FEV_1) from baseline to each post-baseline visit;
- the number of subjects experiencing bronchospasm clinically or spirometrically determined following IMP administration;
- CCI [redacted] from Screening/Randomisation (Visit 1/Visit 2) to Visits 3, 5 and end of treatment (Visit 7) as well as on sputum from Exacerbation Visits and clinic visits due to pneumonia;
- CCI [redacted] from Screening (Visit 1) to End of Treatment (Visit 7);
- haematology, clinical chemistry and renal function tests;
- physical examination and vital signs data;
- 12-lead electrocardiogram.

3 Study Design

3.1 Discussion of Study Design

This is a randomised, multi-centre, double-blind, placebo-controlled, parallel-group interventional trial in subjects with NCFB suffering from chronic infections with *P. aeruginosa*.

The trial will be conducted in approximately 100 sites in up to 15 countries. A total of 420 subjects (210 in each treatment group) are planned to be enrolled into the trial. The enrolment is competitive among sites.

At Visit 2 (within 30 days after Visit 1), eligible subjects with *P. aeruginosa* cultured from an initial sputum sample will be randomised in a 1:1 ratio to receive either colistimethate sodium or placebo.

It is planned that subjects will be contacted by phone 7 days after Randomisation (Visit 2) to determine if there are any issues with IMP administration and/or any initial AEs and will, thereafter, attend 5 further visits at the sites at 1, 3, 6, 9, and 12 months after Randomisation (i.e. Visits 3, 4, 5, 6, and 7) and will have 1 follow-up phone call at 12.5 months. Additional clinic visits, where feasible, and weekly phone calls will be conducted following pulmonary exacerbations until resolution.

The maximum expected duration of participation in the trial for an individual subject, from Visit 1 (Screening) to the follow-up phone call is up to 13.5 months. Treatment duration will be 12 months.

The start of the trial is defined as first subject in, i.e. Visit 1 for the first subject. The end of the trial is defined as the last subject out, i.e. when the last subject has the follow-up phone call.

3.2 Study Treatment

At Visit 2 (within 30 days after Visit 1) eligible subjects with *P. aeruginosa* cultured from their initial sputum sample will be randomised in a 1:1 ratio to receive either colistimethate sodium or placebo.

Subjects will be administered the first dose of the IMP at the investigational site prepared by the site staff and will be instructed by the Investigator or a delegated person how to prepare and self-administer the IMP at home via the [redacted] [redacted] Aerosol Delivery [redacted] system, twice daily (morning and evening) over a period of 12 months. Prior to each administration, a bronchodilator (salbutamol/albuterol) should be taken; if the subject prefers not to use a bronchodilator this should be documented and the lack of bronchial hyper-reactivity after IMP administration documented.

Colistimethate sodium and placebo will be supplied in 30-vial packs.

Colistimethate sodium is supplied as sterile powder in a glass vial. Each vial contains 1,000,000 International Units (1 MIU) which weighs about 80 mg (equivalent to about 33 mg colistin base activity).

Identical sterile vials for placebo will be used. All vials will be masked with white plastic sleeves so that the contents are not visible. The weight of the powder is insignificant compared to the glass vial.

3.3 Study Schedule

The current trial will include 7 planned clinical visits at the investigational site, 1 telephone call 7 days after commencing treatment and 1 follow-up telephone call two weeks after discontinuation of treatment, as detailed in Section 8 of the CTP. A detailed flow chart of CTP Version 7.0 showing the procedures performed is given below in Table 3.3.1.

3.3.1 Trial Flow Chart

ACTIVITIES	Visit 1 Screening/ Rescreening	Visit 2 Randomisation	Phone call	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 EoT	Follow-up phone call	Exacer-bation Visit
	Within 30 Days of Visit 2	Day 0	Day 7	Day 28 ± 1 week	3 months ± 1 week	6 months ± 1 week	9 months ± 1 week	12 months ± 1 week	2 weeks ± 3 days after EoT	------
Informed consent	X									
Medical history/demography	X									
Verify eligibility for randomisation	X	X								
Previous/concomitant medications	X	X		X	X	X	X	X	X	X
AE monitoring including pulmonary exacerbations not otherwise reported	X	X	X	X	X	X	X	X	X	X
[redacted]		X		X	X	X	X	X		
Pregnancy test	X	X		X	X	X	X	X		
Vital signs	X							X		X
Physical examination	X							X		X
12-lead ECG	X							X		
Obtain blood samples: Haematology and clinical chemistry/Renal Function	X			X^a		X		X		
Collect sputum sample	X	X		X		X		X		X
Spirometry: FEV$_1$ and FVC	X	X^b		X	X	X	X	X^b		X
[redacted] **training, dispensing/collection**		X						X		
Review of IMP administration & [redacted] **use (adherence)**		X	X	X	X	X	X	X		
Study medication: Dispense/accountability		X		X	X	X	X	X		
Record of hospitalizations and days of work absence due to pulmonary exacerbations			X	X	X	X	X	X		X

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Weekly follow-up phone calls to determine end of pulmonary exacerbations										X

a Renal function test only.
b FEV$_1$ and FVC to be measured pre-bronchodilator and 30 ± 10 minutes post-IMP dose.

3.4 Concomitant Medication

Permitted concomitant medications are reported in Section 10 of the CTP.

3.5 Study Analysis Populations

There will be 4 analysis populations defined for the trial analyses:

3.5.1 Intention-To-Treat Population

The Intention-To-Treat Population (ITT) will include all subjects who provided informed consent and received a patient number (randomisation number) whether or not they receive IMP.

Following the ITT principle, subjects will be analysed according to the treatment they have been assigned to at randomisation.

3.5.2 Modified Intention-To-Treat Population

The modified ITT (mITT) Population will comprise all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.

Subjects will be analysed according to the treatment they have been assigned to at randomisation.

The mITT will be used to produce summaries of baseline subject characteristics and for the analysis of all primary and secondary efficacy endpoints. Being a double-blind study, no bias due to the exclusion of the non-treated subjects is expected. Exposure variables will also be presented for the mITT.

In addition, the analysis of the mean annual NCFB pulmonary exacerbation rate and the [redacted] will be performed on the subgroup of mITT subjects who were at least 80% adherent as recorded by the [redacted].

3.5.3 Safety Population

The Safety Population will comprise all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of IMP.

Subjects will be analysed according to the treatment they actually received.

The Safety Population will be used to produce summaries of all safety related endpoints and demography.

3.5.4 Per-Protocol Population

The Per-Protocol Population (PP) will include all mITT subjects who were considered compliant with study drug administration (i.e. had an adherence of at least 80%) and who had no major protocol deviations that were considered as potentially impacting the efficacy results.

Major protocol deviations might include, but are not limited to, subjects taking a not-permitted concomitant medication, the IMP not being administered during the trial as defined in the protocol, subjects receiving a treatment different than the one assigned by randomisation. Categories of protocol deviations and additional details are reported in Section 4.10. The exact definition of major protocol deviations impacting the efficacy results will be discussed by the study team during the blind review of the data and described in the Blind Data Review and Analysis Sets Report.

Results of the primary and relevant secondary efficacy endpoints analyses conducted for the PP will be considered as supportive.

3.5.5 Other Populations Defined for Tables and Listings

For the purposes of tables and listings, a further 3 populations are defined:

- All screened subjects: all subjects who provide informed consent;
- Screening failure subjects: all subjects who provide informed consent and are screening failures;
- Enrolled subjects: all subjects who provide informed consent and are not screening failures.

3.6 Withdrawn Subjects

Subjects will be withdrawn from the trial for one of the following reasons:

- subject may withdraw from the study at any time at his/her own request;
- subject may withdraw from the study due to an AE including subjects experiencing a decrease in FEV_1 >15% from pre-bronchodilator baseline and/or clinically determined bronchospasm after receiving their first dose of IMP;
- subject may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative reasons;
- subject may be withdrawn due to lack of adherence to study medication regimen;
- subjects who become pregnant should be withdrawn from the trial;
- non-emergency unblinding of study treatment allocation;
- lost to follow-up: before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study;
- Sponsor, CA, or EC/IRB(s) terminate the trial or participation of an individual site.

The reason for removal of a subject from the trial or premature discontinuation of treatment must be fully documented in the electronic case report form (eCRF) as well as in respective source documents.

Any subject who withdraws after randomisation will not be replaced. Withdrawn subjects will not be re-entered into the study.

3.7 Randomisation

At Visit 2, eligible subjects will be randomised using the interactive web response system (IWRS) according to a pre-specified randomisation scheme such that they either receive colistimethate sodium or placebo. Site and use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No) will be considered as factors for balancing randomisation, i.e. stratification factors. Thus, within each site, subjects with oral macrolides use will be randomised independently from subjects without use of macrolides, to receive colistimethate sodium or placebo in a 1:1 ratio. The randomisation within each site and nested level macrolide use will be done with blocks to guarantee a good balance between colistimethate sodium and placebo at any stage of the enrolment.

Note: according to Exclusion Criterion 15, the decision on whether stable concomitant antibiotic therapy with oral macrolides will be administered to a subject or not will have been taken at least 30 days prior to the Screening Visit (Visit 1). The treatment with oral macrolides should be continued throughout the trial in order not to jeopardize the study results.

3.8 Blinding

Investigational site staff including the Investigator and all personnel involved in study procedures will be blinded to treatment allocation. All Contract Research Organisation (CRO) and Zambon study staff involved in monitoring, data management, or other aspects of the study will also be blinded.

The allocation to treatment will be stored within the IWRS database until unblinding of the trial is requested.

The code for any individual subject will not be broken by the Investigator during the course of the trial except in the circumstance of a Serious Adverse Event (SAE) where knowledge of treatment assignment is essential for the management of patient care. CRO and Zambon Pharmacovigilance can unblind subjects in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the competent authority (CA) and ethics committees (ECs).

The randomisation code will be provided to the Biostatistics group once written authorization of database lock has been received and analysis populations have been defined.

3.9 Sample Size

The sample size was calculated considering the results from the previous trial ([redacted]), relevant literature and the clinically meaningful benefit the treatment should provide. A treatment difference of [redacted] between the colistimethate sodium and placebo groups [redacted]

For the purpose of the power calculation, a simulation of exacerbations was carried out by randomly assigning a patient a value [redacted] according to the treatment group they were in and then generating a [redacted] event rate using this parameter. This [redacted] led to two negative binomials with the following parameter values:

Placebo: mean [redacted], variance [redacted]

Colistimethate sodium: mean [redacted], variance [redacted].

These are rates per year. Note that, since the variances are greater than the mean, this means that there is mild over-dispersion.

Under these assumptions, a [redacted] allowing for over-dispersion for frequency of exacerbation (FOE), with a two-sided significance level of [redacted], a treatment effect of [redacted] and a follow-up time of 1 year, assuming a frequency of [redacted] pulmonary exacerbations per annum for the FOE, a sample size of 170 completed subjects per group would provide a power of 90% (simulated in [redacted] [redacted]1). If the treatment effect size is [redacted] between the colistimethate sodium and placebo groups, the power with [redacted] completed patients per group would be [redacted].

Assuming a drop-out rate of about 20%, the total sample size should be 210 subjects per treatment group (420 total subjects).

A fully blinded reassessment of trial size and power was undertaken for Promis I based on blinded data as of 15th January 2020 in 342 randomised, ITT population subjects. This evaluation gave a blinded annualised exacerbation rate estimate of 1.024 per year and an over-dispersion estimate of 0.273. For the hypothesised [redacted] reduction in the exacerbation rate with colistimethate sodium, this translates to annual event rate estimates for placebo and colistimethate sodium of 1.2701 vs 0.8256. The current data in Promis I, therefore, suggested that n=145 subjects per arm (290 total, unadjusted for dropout) were required to deliver 90% power, as compared to n=170 subjects per arm (340 total, unadjusted for dropout) stated in the protocol. Furthermore, the smallest observed reduction in the exacerbation rate with colistimethate sodium that will yield [redacted] in Promis I was computed to be [redacted].

This recalculation of the sample size was further refined to allow for a reduced overall exposure in Promis I arising due to some subjects dropping out of the study before completing 1 year of follow-up. This leads to a requirement for n =188 subjects per arm (376 total, adjusted for dropout) to detect a [redacted] reduction in the event rate with 90% power as compared to n=210 subjects per arm (420 total, adjusted for dropout) stated in the protocol; and with n =188 subjects per arm, the smallest observed rate reduction to yield [redacted] was computed to be [redacted].

It was, therefore, clear from the blinded data accrued in Promis I subjects to January 2020 that the n = 210 subjects per arm stated in the protocol was unnecessarily high. At worst, the actual number of subjects required in Promis I is n =188 per arm (376 total) and this is inclusive of adjustment for the actual dropout rate seen in the trial itself. Given that, at the time of this sample size reassessment, a total of n =372 subjects had been randomised into Promis I, it could very reasonably be argued that very few, if any, further subjects were actually required to be randomised into the study to provide the required power to test the hypothesis that inhaled colistimethate sodium significantly reduces the exacerbation rate relative to placebo. Recruitment was, therefore, concluded with 377 randomised subjects.

4 Statistical Methodology

4.1 Planned Analyses

The statistical analysis will be performed by [redacted] and will be carried out according to International Conference on Harmonisation (ICH) guidelines ICH E9: "Statistical Principles for Clinical Trials" (CPMP/ICH/363/96 September 1998) and ICH E10 "Choice of Control Group in Clinical Trials" (CPMP/ICH/364/96 January 2001).

All the statistical analyses and outputs will be produced using SAS release 9.4 or later or later (SAS Institute, Inc. Cary, NC, USA).

The data from all countries and all sites will be pooled and summarised. Unless stated otherwise, all available data from withdrawn subjects will be included in the analysis up to the time of withdrawal.

4.1.1 Populations for the Analysis

Demographics and baseline characteristics will be summarised for the mITT population. Demographics and selected baseline characteristics will be also presented for the Safety Population.

The following baseline characteristics will be presented on the mITT Population only:

- Smoking and Alcohol Status
- Non-CF Bronchiectasis History
- Past and Concomitant Relevant Diseases, Diagnosis or Surgeries
- Prior and Concomitant Medication

No baseline testing will be performed.

Primary and relevant secondary efficacy variables will be summarised and analysed for the mITT and PP Population. Results on PP will be considered as supportive.

The number of days of work absence and hospitalisations will be analysed for the mITT population only.

In addition, the analysis on the mean annual NCFB pulmonary exacerbation rate and the [redacted] will be performed considering the subgroup of mITT subjects who were considered adherent i.e. had an adherence of at least 80% (excluding partial doses of ≤12.5% as detailed in Section 4.5.1).

The exposure data will be analysed on the Safety and mITT Populations.

The safety variables will be summarised for the Safety Population.

In case an error occurs in treatment allocation, the following rule will be followed:

- If a subject was randomised but received the incorrect treatment for all the time the subject was in the study, he/she will be reported under the randomised treatment group for all analyses performed on the ITT and on the mITT Population (and in listings on all screened subjects). He/she will be reported under the treatment actually received for all analyses performed on the Safety Population (i.e. an as-treated analysis will be performed). Such subjects will be excluded from the PP Population.

- If a subject received the incorrect treatment after being treated with the correct one, it's foreseen that the subject will be withdrawn from the study. Data for this subject will be analysed until the date of the wrong treatment dispensing. All the data collected after that date will be reported in listings and flagged, but not included in the summary statistics. He/she will be reported under the randomised treatment group for all analyses performed and listings presented.

4.1.2 Treatment Groups

Statistics will be displayed for the following treatment groups:

- Colistimethate Sodium
- Placebo
- Overall

4.1.3 Descriptive Statistics

Descriptive statistics will be used to summarise all efficacy and safety results.

Descriptive statistics for quantitative variables will include n (the number of observations, i.e. non-missing values), mean, standard deviation (SD), median, minimum and maximum values. The 25th and 75th percentiles will also be presented where clearly stated.

Categorical variables will be summarised by using frequency count and percent distributions. Percentages will be calculated using the total number of subjects per treatment/population.

4.1.4 Statistical Significance

The analysis of the trial is on a comparative basis. For all efficacy parameters, comparisons will be made between colistimethate sodium and placebo. Two-sided p-values <0.05 will be considered statistically significant and 95% two-sided confidence intervals (CIs) will be presented where appropriate. No adjustment for multiplicity testing will be adopted. A hierarchical testing procedure will be applied to the secondary endpoints as detailed in Section 4.7.5.

4.1.5 Subgroup Analyses

The mean annual NCFB pulmonary exacerbation rate will also be estimated classifying subjects by:

- Number of NCFB pulmonary exacerbations requiring oral or intravenous antibiotics in the 12 months prior to study entry.

> The number of NCFB pulmonary exacerbations requiring oral antibiotics in the last 12 months and the number of NCFB pulmonary exacerbations requiring intravenous antibiotics in the last 12 months prior to study entry, as collected in the eCRF Screening folder on the Non-CF Bronchiectasis History form, will be summed.

Results will be presented for subjects with 1, 2 and >2 NCFB pulmonary exacerbations in the last 12 months.

If a subject has no data regarding the number of NCFB pulmonary exacerbations requiring oral and/or intravenous antibiotics in the last 12 months prior to study entry the subject will be excluded from the analysis.

- Previous usage of colistimethate sodium/colistin (as collected on the Non-CF Bronchiectasis History eCRF form).

  Based on data collected on the Non-CF Bronchiectasis History eCRF form regarding previous usage of Colistimethate Sodium/colistin, the subjects will be classified into:

  - Without any previous usage of colistimethate sodium/colistin;
  - With previous usage of colistimethate sodium/colistin.

  Subjects with missing data regarding previous usage of colistimethate sodium/colistin will be excluded from the analysis.

CCI [redacted] will be presented classifying subjects by status of previous usage of colistimethate sodium/colistin as collected on the Non-CF Bronchiectasis History eCRF form. Subjects with missing data regarding previous usage of colistimethate sodium/colistin will be included in the analysis in a separate subgroup.

4.1.6 Definition of Baseline

Age, height, weight and Body Mass Index (BMI) recorded at Visit 1 will be presented as baseline characteristics.

For 12-lead ECG, vital signs, physical examination and haematology, clinical chemistry and renal function parameters, baseline values are those recorded at Screening (Visit 1). If no assessment has been conducted at that visit, the last available value before IMP first dose (collected during unscheduled visits before IMP first dose) will be considered as baseline.

For sputum analysis, CCI [redacted] and spirometry baseline values are those recorded at Visit 2 before IMP first dose. If no assessment has been conducted at that visit, the last available value before IMP first dose (collected at the Screening visit or unscheduled visits before IMP first dose) will be considered as baseline.

4.1.7 Definition of Follow-up Time

All the efficacy analyses are focused on the endpoints collected during the treatment period. For these analyses, the follow-up time will not include the time from end of treatment to the follow-up call.

The follow-up time in days will be calculated using the following formula:

- Follow-up time (days) = [date of treatment completion/discontinuation - date of first IMP dose + 1].

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

- Follow-up time (years) = Follow-up time (days) / 365.25.

Date of treatment completion will be the date of End of Treatment Visit.

Date of treatment discontinuation will be the date of End of Study Visit for subjects who discontinued the study before the End of Treatment Visit. In case a subject is lost to follow-up, the date of treatment discontinuation will be the date of last Study Visit.

Date of last Follow-up will not include any visits/calls after the end of treatment.

4.1.8 Visit Dates

For each visit, the date recorded by the Investigator in the eCRF (variable SVSTDTC in the SDTM SV domain) will be considered as the visit date in all the algorithms and the listings.

4.1.9 Date of First/Last IMP Dose

The date of first IMP dose is the earliest date of IMP dose considering both the eCRF and the recordings from the CCI logging system.

The date of last IMP dose is derived as follows. Where CCI data is available for the subject, the date of last IMP dose will be defined as the latest date from the CCI logging system, with the following exception. Due to the Covid-19 pandemic, for some subjects, Visit 7 was split into a remote phone call (at the scheduled time of treatment completion), followed by an in-clinic visit (for the purpose of collecting pre-dose and post-dose spirometry data to test for bronchospasm). In such cases, the scheduled study treatment period was completed at the time of the remote Visit 7 phone call, but an additional IMP dose was given at the time of the in-clinic Visit 7. In these circumstances, the latest date from the CCI logging system will be compared to the penultimate date from the CCI logging system and, if the latest date is more than 14 days after the penultimate date (latest date – penultimate date >14), the CCI logging system data will be used taking into consideration the penultimate IMP dose as the date of last IMP dose. The date of last IMP dose will be defined as the date of last IMP administration as entered on the End of Study eCRF form only when CCI data is unavailable.

Any inconsistency between eCRF and CCI logging system data will be discussed before the database lock.

4.1.10 Data Re-Allocation

Data collected at the early termination visit (when used) for discontinued subjects will not be re-allocated. Early termination data will not be moved in the database, however, statistical programming will allocate this visit as Visit 7 within the Analysis Data Model (ADaM) datasets.

Potential issues of the approach defined above and other decisions regarding data re-allocation will be evaluated during the blind review of the data and documented in the Blind Data Review and Analysis Sets Report.

4.1.11 Exclusion of Data from the Statistical Analysis

If a subject received the incorrect treatment after being treated with the correct one, all the data collected after the date of the wrong treatment dispensing will be reported in listings and flagged, but not included in the statistical analysis on the ITT, mITT, Safety and PP populations.

Where not stated differently, assessments conducted at an early termination visit and unscheduled assessments will not be considered in the statistical analysis, but will be listed only.

Only NCFB pulmonary exacerbations with a start date ≥ date of first IMP dose and ≤ date of treatment completion/discontinuation will be considered in the analysis.

In case of data excluded from the statistical analysis (in the situations described above but also in other cases, for example: spirometry tests excluded due to technical issues, or assessment not done), the derived variables based on these data will not be calculated. For example, the change from baseline to Visit 5 will not be calculated if the measurement at Visit 5 is excluded from the statistical analysis, or all the changes from baseline will not be calculated if the measurements pre-dose are excluded.

4.1.12 Listings

All data collected will be presented in the listings.

4.2 Interim Analysis

No interim analysis is planned for this study.

4.2.1 Data CCI

Due to the impact of Covid-19 during the conduct of the study, the Sponsor has established a CCI Committee CCI to evaluate the impact of decisions made CCI on the integrity of the study data. Although the CCI will only review blinded data, the CCI will advise if additional CCI analyses may be needed as a result of this pandemic. In addition, the CCI will review blinded pulmonary exacerbation data to determine whether or not events have been correctly assigned as meeting protocol-defined criteria. The CCI may recommend that sites reconsider their classification of pulmonary exacerbations as meeting the protocol-defined criteria or not (as well as re-examine the duration of the event based on the existing eCRF data), however, the ultimate decision will remain that of the Principal Investigator at each site.

For clarification purposes (and the generation of relevant data queries to sites), a further clarification to the protocol definition for pulmonary exacerbations has been provided as follows:

- the presence of 3 or more pre-defined symptoms / signs[1] within any 24-hour period[2]

and

- the episode of exacerbation lasted for at least 24 hours[3]

and

- in the opinion of the Investigator, the subject required and started treatment with systemic antibiotics

Explanatory notes:

[1] The pre-defined symptoms / signs are: increased cough; increased sputum volume and / or consistency; increase sputum purulence; new or increased haemoptysis; increased wheezing; increased dyspnoea; increased fatigue / malaise; episodes of fever (≥38°C or ≥100.4°F).

[2] The pre-defined symptoms / signs need to occur within the same 24-hour period (and this defines the start date of the Protocol-Defined Exacerbation) but do not need to be present at exactly the same time.

[3] The overall episode of exacerbation needs to last at least 24 hours, but individual symptoms / signs can last less than 24 hours (for example, a temperature).

4.3 Disposition of Subjects

The number of subjects screened and the number of screen failures will be presented (overall). All screened subjects will be included. Re-screened subjects will be counted twice in the number of screened subjects. The number of re-screened subjects will be presented.

The number and percentage of randomised subjects who completed the study, withdrew from the study after randomisation and the number and percentage of subjects with each reason for withdrawal from the study will be presented by treatment group for the ITT population. Summaries of enrolled subjects will be reported overall and by country. These will include a presentation of country, number of subjects randomised and number of subjects who completed the study for the ITT population.

The number and percentage of subjects at Visit 2, who attended Visits 3, 4, 5, 6 and 7 and who had a follow-up call will be presented by treatment group and overall for the mITT Population. Time to completion/discontinuation from the study (days) will be summarised by descriptive statistics and calculated as (date of completion/discontinuation – date of first IMP dose).

The number and percentage of screened subjects who had any inclusion/exclusion criteria deviation as detailed in the eCRF will be reported. Results will be presented also for each criterion.

Protocol deviations affecting the efficacy analyses and protocol deviations specifically related to the COVID-19 pandemic will also be summarised for the Enrolled Population. The number and percentage of subjects included in each analysis population will be presented overall and by treatment group.

4.4 Baseline and Demographic Characteristics

No formal comparison between treatment groups on baseline and demographic characteristics will be done. Unless specifically stated in the relevant section, analysis will be done on the mITT Population.

4.4.1 Demography Characteristics

Demographics will be summarised by treatment group and overall. This will include age, ethnicity, gender, race, employment status, height (cm), weight (kg), BMI (kg/m^2).

Summaries will be produced using the mITT and the Safety Population.

Note:

- Age, height, weight, BMI and employment status recorded at Visit 1 will be presented.

4.4.2 Smoking and Alcohol Status

Smoking status at Screening (non-smoker, former smoker or current smoker), will be presented by treatment group and overall for the mITT Population. Former smoker will be further characterised summarising time from last cigarette (years) and number of pack-years.

Alcohol Status (Alcohol consumer: Yes or No) at Screening will be presented by treatment group and overall, along with summaries of alcohol units per week for alcohol consumers.

Notes:

- For former smokers, time from last cigarette (years) will be calculated as (screening date – date of last cigarette)/365.25;
- In order to calculate the time from last cigarette, the following rules will be applied for partial dates of the last date of smoking:
    - if only the day is missing, the first day of the month will be assumed;
    - if the day and the month are missing, then the first day of the year will be assumed.

4.4.3 Non-CF Bronchiectasis History

The following variables will be summarised for the mITT Population by treatment group and overall:

- Time since diagnosis of non-CF bronchiectasis (years);
- Diagnostic technique used (computerised tomography [CT] or high resolution CT: Yes or No);
- Number of lobes affected (1, 2, 3, more than 3);
- Underlying cause of the bronchiectasis;
- Number of NCFB pulmonary exacerbations requiring oral antibiotics in the last 12 months before Screening;
- Number of NCFB pulmonary exacerbations requiring intravenous antibiotics in the last 12 months before Screening;
- Previous usage of colistimethate sodium/colistin;
- Having at least 1 positive sputum culture for *P. aeruginosa* before Screening.

Notes:

- Time since diagnosis of NCFB (years) will be calculated as (date of Visit 1 – date of diagnosis of NCFB)/365.25;
- In order to calculate the time since diagnosis of NCFB, the following rules will be applied for partial dates of the date of diagnosis of NCFB:
    - if only the day is missing, the first day of the month will be assumed;
    - if the day and the month are missing, then the first day of the year will be assumed.

4.4.4 Past or Concomitant Relevant Diseases, Diagnoses or Surgeries

Past or concomitant relevant diseases, diagnosis or surgeries will be summarised by system organ class (SOC) and preferred term (PT), by treatment group and overall using the mITT Population.

Notes:

- Past or concomitant relevant Diseases, Diagnoses or Surgeries will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher;
- Past relevant Diseases, Diagnoses or Surgeries are defined as records in the Medical History eCRF form which are not ongoing at Visit 1;
- Concomitant relevant Diseases, Diagnoses or Surgeries are defined as records in the Medical History eCRF form which are ongoing at Visit 1;
- Terms will be displayed in descending overall frequency (and then alphabetically) of SOCs and in descending overall frequency (and then alphabetically) of PTs within each SOC.

4.4.5 Spirometry at Visit 1 and Pre-Dose at Visit 2

The following spirometry parameters will be summarised by treatment group and overall:

- FEV_1 (L);
- Predicted FEV_1 (%);
- FVC (L);
- Predicted FVC (%).

Spirometry results assessed at Visit 1 and at Visit 2 Pre-dose will be summarised using summary statistics for continuous variables. Summaries will be provided for the mITT and for the Safety Population. Results for the Safety Population will be presented along with summaries for spirometry parameters assessed during Visits 3 – 7, inclusive.

More details of the analysis are reported in Section 4.8.2.

4.4.6 Haematology, Clinical Chemistry and Renal Function Parameters at Visit 1

Haematology, clinical chemistry and renal function parameters assessed at Visit 1 will be listed.

More details of the analysis are reported in Section 4.8.4.

4.4.7 Vital Signs at Visit 1

Respiratory rate (breaths per minute), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg) and body temperature (°C) assessed at Visit 1 will be listed.

More details of the analysis are reported in Section 4.8.5

4.4.8 Physical Examination at Visit 1

Physical Examination findings collected at Visit 1 will be listed.

More details of the analysis are reported in Section 4.8.6.

4.4.9 12-Lead ECG at Visit 1

The 12-lead ECG overall interpretation at Visit 1 will be listed.

More details of the analysis are reported in Section 4.8.7.

4.4.10 Pregnancy Test

Results from the dipstick urine pregnancy test for women of child-bearing potential will be listed only.

4.4.11 Presence of *P. aeruginosa* in Sputum at Visit 1

Number and percentage of subjects with presence of [redacted] collected at Visit 1 will be reported for the mITT Population. Subjects with results <20CFU/mL will be considered as negative based on the central lab specifications. The local laboratory result will just record presence or absence of *P. aeruginosa* for eligibility purposes only. The number and percentage of subjects with presence of [redacted] as collected in the eCRF will be presented.

4.4.12 [redacted] and [redacted]

The [redacted] total score and domain scores and the [redacted] domain scores at Visit 2 (see Sections 4.7.6.2 and 4.7.6.9 for further details regarding the calculation of the [redacted] and [redacted]) will be summarised by treatment group and overall using the mITT Population and the PP Population for [redacted] and the mITT Population only for [redacted] (see Section 4.7.5). Results will be presented along with summaries for results at Visits 3 – 7, inclusive.

4.5 Exposure

4.5.1 Number and Duration of Inhaled Doses

An inhaled dose is defined as any complete or partial dose of IMP that the subject inhaled either at the investigational site or at home (excluding doses ≤12.5% as recorded in the [redacted] logging system and any final dose recorded in the [redacted] logging system that is more than 14 days after the penultimate dose in the [redacted] logging system where Visit 7 was split due to Covid-19, as described in Section **Error! Reference source not found.**).

For doses administered at the investigational site, inhaled doses are all doses with a date of administration filled in the "IMP administration under clinical supervision" eCRF page. Complete doses are those recorded as complete in the eCRF. Partial doses are those recorded as non-complete in the eCRF.

For doses administered at home, inhaled doses are all doses with a date and time of administration recorded in the [redacted] logging system and dose different than "Null" or "≤12.5%".

The overall number of inhaled doses either at the investigational site or at home will be summarised along with their duration. For doses administered at the investigational site only, the number of complete and partial doses will also be reported.

Summaries will be presented for the Safety and mITT Populations.

Notes:

- All the doses will be recorded in the [redacted] logging system, regardless of being administered at the investigational site or at home. Doses administered at home are those not recorded in the eCRF. In case of any inconsistencies between eCRF and [redacted] data, the [redacted] data will be used in the analysis. While missing date/time of doses might be present in the eCRF, [redacted] data are expected to be complete.

4.5.2 Exposure Days

An Exposure Day (ED) is defined as any day that the subject inhaled at least one full or partial dose of IMP as defined in Section **Error! Reference source not found.**, either at the investigational site or at home regardless of the number of doses on that day. The number of EDs per subject will be summarised overall and by treatment group for the Safety and mITT Populations using descriptive statistics for continuous variables.

4.5.3 Extent of Exposure

Extent of exposure (days) will be calculated using the following formula:

- Extent of exposure (days) = Date of last full or partial inhaled dose of IMP - date of first full or partial inhaled dose of IMP + 1.

The date of last full or partial inhaled dose of IMP is as defined in Section **Error! Reference source not found.**.

The extent of exposure will also be calculated in weeks using the following formula:

- Extent of exposure (weeks) = Extent of exposure (days) / 7.

Dose of IMP either at the investigational site or at home will be considered.

Treatment exposure will be summarised overall and by treatment group for the Safety and mITT Populations using descriptive statistics for continuous variables.

4.5.4 Adherence

Adherence will be calculated overall.

The evaluation of adherence will be based on the following formula:

- Adherence (%) = (# Total Inhaled Doses / # Scheduled Doses)*100.

The total number of inhaled doses of IMP will be computed as described in Section 4.5.1. In cases where, due to the Covid-19 pandemic, the final dose registered on the [redacted] device is the dose given at the in-clinic part of a split Visit 7 for the purposes of bronchospasm testing, any dose on the [redacted] that is later than the date of last IMP administration as entered on the End of Study eCRF form will not be counted as an inhaled dose for the calculation of IMP adherence.

The scheduled doses will be computed as 2 times the total number of days from Visit 2 to the end of period date, i.e. (End of period date – date of Visit 2) + 1.

For the overall adherence, the end of period date will be the date of the last inhaled dose of IMP, based on the latest of the last dose recorded in the [redacted] download (with the exceptions noted above relating to split Visit 7's) or the date of the last dose of IMP recorded in the End of Study form in the eCRF.

Adherence will be summarised by treatment group and overall for the mITT Population, presenting descriptive statistics for continuous variables and absolute and relative percentages of subjects considered to be adherent, i.e. with a least 80% of adherence.

An additional summary displaying the number and percentage of subjects in the following categories will also be presented by treatment group:

- <60%;
- 60 to <70%;
- 70 to <80%;
- 80 to <90%;
- ≥90%.

4.5.5 IMP interruptions

The number and percentage of subjects with at least one IMP interruption, the number and percentage of subjects with at least one IMP interruption due to NCFB pulmonary exacerbation and the number of NCFB pulmonary exacerbations which lead to an IMP interruption will be presented.

Moreover, the number of days of IMP interruption overall and due to NCFB pulmonary exacerbations will be summarised using descriptive statistics for continuous variables.

Results will be presented overall and by treatment group for the Safety and mITT Populations.

Notes:

- NCFB pulmonary exacerbations will be linked to the corresponding AE using the AE number collected in the eCRF form "Pulmonary Exacerbation", i.e. "Please specify corresponding Adverse Event number for this Pulmonary Exacerbation".
- IMP interruption (days) will be calculated considering stop date and re-start date of IMP as collected in the eCRF "Adverse Event" form using the following formula:

  IMP interruption (days) = Re-Start date of IMP - date of Stop of IMP + 1.
- If any dose with a dose different than "Null" is recorded in the [redacted] logging system during this period, then the [redacted] data will be considered to compute IMP interruption: stop date will be the last IMP dose date before the start of the AE, re-start date will be the first IMP dose date after the start date of the AE.

4.6 Prior and Concomitant Medication

The incidence of prior and concomitant medications will be presented by therapeutic area according to the Anatomical Therapeutic Chemical (ATC) level 4 classification and preferred drug name, by treatment and overall for the mITT Population.

Prior medications are those that started and stopped before exposure to IMP; concomitant medications are all medications taken during the study period, including those started before but on going at first IMP dose.

Where a medication start/stop date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Notes:

- Prior and concomitant medications are all medications collected in the eCRF forms Prior and Concomitant Medications and Systemic Antibiotic Therapy.
- Medications are coded using the World Health Organisation (WHO) Drug Dictionary, WHO-DD (please refer to the final Data Management Plan for the latest coding information);
- Only the number of subjects with medications (not the number of medications) will be presented;
- If a subject has multiple occurrences of a medication, the subject will be presented only once in the respective subject count;
- Prior and concomitant medications will be summarised in separate tables;
- Medications will be displayed in descending ATC text and drug name frequency overall and then alphabetically.

4.7 Efficacy / Primary and Secondary Analysis

The analysis of the trial is on a comparative basis. For all efficacy parameters, summaries will be presented by treatment group and comparisons will be made between colistimethate sodium versus placebo. Two-sided p-values <0.05 will be considered statistically significant and 95% two-sided CIs will be presented, where appropriate.

Primary and secondary efficacy variables, where not stated differently, will be summarised for the mITT and, where relevant, PP Populations. The primary analysis will be performed on the mITT Population. Analyses conducted using the PP will be considered supportive.

The health economic variables will be analysed on the mITT Population only.

In addition, the analysis of the mean annual NCFB pulmonary exacerbation rate and the CCI [redacted] will also be performed considering the subgroup of mITT subjects who were considered adherent, i.e. had an adherence of at least 80%.

4.7.1 Primary Endpoint

The primary endpoint of this trial is the mean annual NCFB pulmonary exacerbation rate. The annual NCFB pulmonary exacerbation rate will be computed for each subject as follows:

- Annual NCFB pulmonary exacerbation rate = number of NCFB pulmonary exacerbations / follow-up time (years)

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Where NCFB pulmonary exacerbations are defined in Section 4.7.4 and follow-up time is computed as detailed in Section 4.1.7.

A pulmonary exacerbation is defined as the presence concurrently of at least 3 of the following 8 symptoms/signs for at least 24 hours:

- increased cough;
- increased sputum volume and/or consistency;
- increased sputum purulence;
- new or increased haemoptysis;
- increased wheezing;
- increased dyspnoea;
- increased fatigue/malaise;
- episodes of fever (temperature ≥38°C);

And it is clinically determined that the subject requires and is prescribed systemic antibiotic therapy.

4.7.2 Normality Assumption Checking

Not applicable.

4.7.3 Closed Testing Procedure for Primary Analysis

Not applicable.

4.7.4 Method of Analysis for Primary Endpoint

The NCFB pulmonary exacerbations collected from the Pulmonary Exacerbation eCRF form will be considered for the analysis. All cases in which the variable "Do these symptoms meet the protocol-defined criteria for NCFB pulmonary exacerbation?" is not consistent with data collected in the corresponding eCRF Pulmonary Exacerbations Symptoms form will be discussed during the blind review meeting. The decisions taken will be documented in the Blind Data Review and Analysis Sets Report.

The start of a protocol-defined NCFB pulmonary exacerbation will be taken as the first day that at least 3 of the 8 defining symptoms occurred concurrently for at least 24 hours as determined by the Investigator, as documented by the start date of the corresponding AE in the eCRF Adverse Events form and reviewed, where necessary, by the DAC (see Section 4.2.1) taking into consideration aspects such as start/stop date and associated systemic antibiotic therapy/hospitalisations.

Only NCFB pulmonary exacerbations with start date ≥ date of first IMP dose and ≤ date of treatment completion/discontinuation will be considered in the analysis. NCFB pulmonary exacerbations with start date = date of first IMP dose will be discussed on a case-by-case basis during the blind review of the data in order to evaluate whether they should be classified as having occurred in the screening period. The decisions taken will be documented in the Blind Data Review and Analysis Sets Report.

Resolution of a NCFB pulmonary exacerbation is defined as the date of completion of the required course(s) of antibiotic treatment, as collected in the eCRF Systemic Antibiotic Therapy form, and/or the Investigator's judgement that the NCFB pulmonary exacerbation has resolved, as documented by the end date provided for the corresponding AE in the eCRF Adverse Events form, whichever is the later of the two dates. If more than one systemic antibiotic therapy is administered for a NCFB pulmonary exacerbation, then the latest end date will be considered as the date of completion of the required course of antibiotic treatment.

In the case of a partial onset date of NCFB pulmonary exacerbation due to missing day, the onset of the event will be assumed to be the first day of the month. If the resultant derived date is prior to the date of first IMP dose, then it will be assumed to be equal to the first IMP dose date. Resultant derived dates will be reviewed during the blind review meeting and documented in the Blind Data Review and Analysis Sets Report.

In case of a partial resolution date of NCFB pulmonary exacerbation due to missing day, the resolution of the event will be assumed to be the last day of the month. If the resultant derived date is after the treatment completion/discontinuation date, then it will be assumed to be equal to the treatment completion/discontinuation date.

In case a NCFB pulmonary exacerbation presents a symptom with missing duration, following a conservative approach, the longest duration based on the start and stop dates of that symptom and until the resolution date of the NCFB pulmonary exacerbation will be imputed.

Two NCFB pulmonary exacerbations will be considered as a single episode in the statistical analysis if the second exacerbation started less than 14 days after the end of the systemic antibiotic therapy for the previous exacerbation (start date of the exacerbation - end date of the treatment of the previous exacerbation < 14 days). In case of more than two exacerbations for the same subject, this rule will be applied iteratively (therefore, more than two exacerbations may be considered as a single episode). Such cases will be discussed during the blind review of the data and the decisions taken will be documented in the Blind Data Review and Analysis Sets Report.

The above rule will not apply to the analysis of NCFB pulmonary exacerbations as AEs in the safety analysis.

In case of NCFB pulmonary exacerbations considered as a single episode:

- the start date of the first event will be considered as the start date;
- the stop date of the last event will be considered as the stop date;
- a worst case approach will be considered for duration of symptoms and requirement of hospitalisation. For example, if one of two exacerbations considered as a single episode has/have increased dyspnoea for ≥24 hours and <48 hours and the other one has increased dyspnoea for ≥ 48 hours, the single episode will be considered in the analysis as having dyspnoea for ≥ 48 hours.

In order to investigate whether the use of inhaled colistimethate sodium reduces the frequency of pulmonary exacerbations compared to placebo in subjects with NCFB chronically infected with *P. aeruginosa,* the following hypothesis will be tested:

- Null hypothesis: there is no difference between inhaled colistimethate sodium and placebo as regards the effect on the pulmonary exacerbation rate

- Alternative hypothesis: inhaled colistimethate sodium reduces the pulmonary exacerbation rate in favour of inhaled colistimethate sodium compared to placebo.

The null hypothesis must be rejected for the efficacy of inhaled colistimethate sodium to be considered demonstrated.

The number and the percentage of subjects with NCFB pulmonary exacerbations, the number of NCFB pulmonary exacerbations and the total follow-up time in years, as defined in Section 4.1.7, will be summarised by treatment group.

The number of NCFB pulmonary exacerbations during the treatment period will be analysed using a negative binomial model including treatment, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as fixed effects and log-time on treatment as an offset. If there is a significant p-value ($p<0.05$) observed for the country covariate in this primary analysis then the number of NCFB pulmonary exacerbations during the treatment period will also be analysed using a negative binomial model for each country separately with use of stable concomitant therapy with oral macrolides as a fixed effect and log-time on treatment as an offset.

The adjusted mean annual NCFB pulmonary exacerbation rates in each treatment group and the adjusted rate ratio with their 95% CIs will be estimated by the model. OBSMARGINS option will be used for the estimates. The number of subjects considered in the model will be provided by treatment group. An adjusted rate ratio <1 will indicate that colistimethate sodium decreases the rate of pulmonary exacerbations compared to placebo. A two-sided Wald chi-square test p-value of <0.05 will be considered statistically significant. P-values of the effects based on Wald chi-square test will also be presented.

The log-time on treatment in years will be calculated using the following formula:

- Log-time on treatment = ln (Follow-up time).

The number and the percentage of subjects with 0, 1, 2 or >2 pulmonary exacerbations will be presented.

The number and the percentage of subjects with pulmonary exacerbations, the number of pulmonary exacerbations and the pulmonary exacerbation rate per subject per year will also be presented by treatment group for severe (defined as those requiring intravenous antibiotics and/or hospitalisation) and not severe exacerbations.

The rate of pulmonary exacerbations per subject per year will be calculated for each treatment using a weighted approach (which consists of pooling all subjects in a treatment group and dividing the total number of pulmonary exacerbations by the total follow-up time).

The total duration of systemic antibiotic therapy, overall and by route, will be summarised by treatment group using descriptive statistics for continuous variables as well as distribution frequencies for the following categorisations:

- 1-7 days;
- 8-15 days;
- 16-30 days;
- >30 days;
- Not Evaluable.

Results will be reported overall and by country.

The duration of the treatment will be evaluated considering the start and end date of the therapy associated with the pulmonary exacerbation. The duration of each course of systemic antibiotic therapy will be calculated using the following formula:

- Duration (days) = stop date – start date +1

For exacerbations treated with more than one systemic treatment, the duration will be calculated by summing the duration of the associated treatments. The overlapping days will be counted only once.

It is expected that all systemic antibiotic therapy will have completed (i.e. will have a stop date) at the end of the study when data are final, as all therapy stop dates are required to be known in order to derive the resolution date of pulmonary exacerbations per the definition described earlier in this section.

In order to calculate the duration of each course of systemic antibiotic therapy, the following rules will be applied for partial dates of start and stop date of systemic antibiotic therapies:

For the start date:

- if only the day is missing, the first day of the month will be assumed. If the resulting derived date is prior to the start date of the exacerbation, then start date of therapy will be assumed to be equal to the start date of the pulmonary exacerbation.
- if the day and the month are missing, then the date will not be imputed and the duration will be classified as "Not Evaluable".

For the stop date:

- if only the day is missing, the last day of the month will be assumed;
- if the day and the month are missing, then the date will not be imputed and the duration will be classified as "Not Evaluable".

Resultant dates will be discussed during the blind review meeting and documented in the Blind Data Review and Analysis Sets Report.

The above summary/analysis will be performed using the mITT Population and, where appropriate, the PP Population. Results for the PP Population will be considered as supportive.

4.7.4.1 CCI Analysis Using Alternative Definition of NCFB Pulmonary Exacerbation

A CCI analysis will be conducted using an alternative definition of NCFB pulmonary exacerbation for the mITT Population. The re-classification of pulmonary exacerbations will be done during the blind review meeting and documented in the Blind Data Review and Analysis Set Report.

In this CCI analysis, a NCFB pulmonary exacerbation is defined as deterioration in three or more of the following key symptoms for at least 48 hours:

- Cough;
- Sputum volume and/or consistency;

- Sputum purulence;
- Breathlessness and/or exercise tolerance (dyspnoea);
- Fatigue and/or malaise;
- Haemoptysis;

And:

a physician determines a change in bronchiectasis treatment is required when other potential causes of clinical deterioration have been discounted, i.e. the subject requires a systemic antibiotic therapy due to the NCFB pulmonary exacerbation.

Subjects experiencing NCFB pulmonary exacerbations according to this alternative definition will be identified as those subjects having:

- An AE on the eCRF Adverse Events form with a MedDRA coded Preferred Term of "infective exacerbation of bronchiectasis" that is at least 48 hours in duration (i.e. stop date of AE – start date of AE + 1 ≥ 2);
- At least 3 of the above symptoms on the eCRF Pulmonary Exacerbation Symptoms form for the Pulmonary Exacerbation Number corresponding to that AE, where those symptoms all occur between the start and stop dates of the AE;
- At least 1 therapy on the eCRF Systemic Antibiotic Therapy form for the Pulmonary Exacerbation Number corresponding to that AE.

Analysis will be conducted following the same rules and methods as detailed above for the main definition of NCFB pulmonary exacerbations.

4.7.4.2 [redacted] Analysis for Discontinuers

In order to assess the potential impact of missing data on the results of the primary efficacy analysis, [redacted] analyses based on multiple imputation (MI) will be performed on all mITT subjects based on the approach proposed by Keene et al. [1].

For all subjects with a follow-up duration shorter than 365 days (i.e., 52 weeks + 1 day), the number of pulmonary exacerbations from the end of the follow-up period up to day 365 will be imputed.

The imputation model will include the following variables: treatment, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides.

The imputation will be performed according to the following strategies:

- missing at random: imputation based on the Missing At Random (MAR) assumption in all treatment groups. This analysis is based on the same assumption behind the model used for the primary efficacy analysis, however, it will allow for the inclusion in the analysis of all mITT patients;
- copy reference: imputation based on the data distribution of the placebo group in both treatment groups. This analysis mimics the case where discontinued subjects are in effect non-responders.

One thousand imputations will be performed and the analysis of the total number of pulmonary exacerbations (observed + imputed events) will be based on the same negative binomial model used for the primary efficacy analysis. Estimates from the models will then be combined using Rubin's rule [2].

4.7.4.3 CCI Analysis on Adherent Subjects

The primary analysis will also be repeated considering the subgroup of mITT subjects who were considered adherent, i.e. had an adherence of at least 80%.

4.7.4.4 Further Investigation: Number of Pulmonary Exacerbations in the 12 Months Prior to Study Entry

To further investigate any possible factor that might affect the mean annual NCFB pulmonary exacerbation rate, an exploratory negative binomial model will be fitted for the mITT population considering as an extra covariate the number of NCFB pulmonary exacerbations requiring oral or intravenous antibiotics in the 12 months prior to study entry.

4.7.4.5 Further Investigation: Stratified Analysis by Number of Pulmonary Exacerbation Requiring Oral or Intravenous Antibiotics in the 12 Months Prior to Study Entry

The number of NCFB pulmonary exacerbations requiring oral antibiotics in the last 12 months and the number of NCFB pulmonary exacerbations requiring intravenous antibiotics in the last 12 months prior to study entry, as collected in the eCRF Screening folder on the Non-CF Bronchiectasis History form, will be summed.

Analysis will be performed with the same criteria and methods as described for the primary efficacy model. If a subject has no data regarding the number of NCFB pulmonary exacerbations requiring oral and/or intravenous antibiotics in the last 12 months prior to study entry the subject will be excluded from the analysis.

A stratified analysis will also be performed classifying subjects according to the number of pulmonary exacerbations requiring oral or intravenous antibiotics in the 12 months prior to study entry, as reported in Section 4.1.5.

4.7.4.6 Further Investigation: Stratified Analysis by Previous Usage of Colistimethate Sodium/Colistin

A stratified analysis will also be performed by previous usage of colistimethate sodium/colistin (as collected on the Non-CF Bronchiectasis History eCRF form) as reported in Section 4.1.5.

4.7.4.7 Further Investigation: Prentice, Williams and Peterson model

A Prentice, Williams and Peterson (PWP) model for total time will be fitted to further investigate any possible effect of correlation between events on the study results. If the correlated nature of the events is ignored, the CIs for the estimated rates could be artificially narrow [3]. Hence, in this further analysis, adjustments for within-individual correlation will be applied fitting the PWP model.

The model will include treatment group, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as covariates.

The data will be limited to a maximum number of recurrence events in order to avoid unreliable and unstable estimates. The maximum number of events considered in the model will be set up to include the full set of events for at least 90% of the subjects, i.e. 90% of the subjects having at most this number of pulmonary exacerbations.

Hazard ratio and corresponding 95% CIs for treatment group will be presented.

4.7.4.8 Further Investigation: Non-Parametric ANCOVA Model on Ordered Score for Number of Pulmonary Exacerbations

An additional analysis will be carried out on a NCFB pulmonary exacerbation score applying a non-parametric analysis of covariance (ANCOVA) model with a randomisation-based methodology as proposed by Koch et al [4]. Considering the sample size foreseen for this analysis, there won't be any correction for type I error.

Subjects will be classified with a NCFB pulmonary exacerbation score of 0, 1 or 2, depending on their individual yearly rate of NCFB pulmonary exacerbations.

The individual yearly rate of NCFB pulmonary exacerbations will be calculated for each subject using the following formula:

- Individual yearly rate = number of NCFB pulmonary exacerbations / follow-up time (years).

The NCFB pulmonary exacerbation score will be:

0 if individual yearly rate = 0

1 if 0 < individual yearly rate ≤ 1

2 if individual yearly rate > 1

The model will include treatment group, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as covariates. No stratification variable will be included.

Treatment effect, i.e. the increase in the overall score for the active colistimethate sodium versus placebo, will be presented along with the standard error, associated test statistic and two-sided p-value. Additionally, the asymptotic 95% CI for the treatment estimate will be reported. Due to the fact that the p-value computation is based on the re-randomisation of the population, while CI is based on repeated random sampling theory there might be disagreement regarding the treatment effect using these two different approaches. Even if these occurrences are quite infrequent, it is worth stating that the p-value from the randomisation test is based on a more realistic and minimal assumption and should take precedence [5].

Individual yearly rate of NCFB pulmonary exacerbations and NCFB pulmonary exacerbation score will be presented in a listing. NCFB pulmonary exacerbation score will also be summarised presenting the number and percentages of subjects with a score of 0, 1 or 2.

4.7.5 Secondary Endpoints

A hierarchical testing procedure will be applied to the secondary endpoints of this study, as per the following order:

- CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

No test will be considered significant in this hieararchy unless every earlier test in it, including that for the primary outcome, is significant. For the purposes of this SAP, it is anticipated that only the time to first pulmonary exacerbation and [redacted] total scores will be analysed for the PP Population in addition to the mITT Population.

4.7.6 Methods of Analysis for Secondary Endpoints

4.7.6.1 [redacted]

The [redacted] will be calculated as the time in days from the date of the first dose of IMP to the date at which the [redacted].

- Time to [redacted] = start date of [redacted]. (It should be noted that this differs slightly from the [redacted]. For time-to-event endpoints, generally the + 1 is not included because this overestimates the time by 1 day for every event.)

Subjects completing the trial without [redacted] or who are discontinued prematurely [redacted], will be considered as censored at the time of their last follow-up, i.e. at the date of treatment completion/discontinuation. For the analysis, the following formula will be applied:

- Censoring time (days) = (date of treatment completion/discontinuation - date of the first dose of IMP)

Kaplan-Meier estimates in each treatment group will be presented: median time to [redacted], 25th and 75th percentiles and the corresponding CIs will be tabulated. The number of [redacted] [redacted] [redacted] subjects at the beginning of the period, the cumulative number of subjects with [redacted] at the end of the period and the estimated rates of pulmonary exacerbations at the end of the period with the associated 95% CIs will be presented by treatment group for the following study periods: (0-28] days, (28-90] days, (90-180] days, (180-270] days and (270 days - End of Treatment] as supportive statistics.

The estimate of the survivor function in each group will be displayed graphically using a Kaplan-Meier curve.

For the main analysis, a log-rank sum test will be used to compare the survival distributions of the two treatment groups. A two-sided p-value of <0.05 will be considered statistically significant.

A Cox proportional hazard regression model will be used to compare the treatment groups as supportive analysis. The model will include treatment group, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as covariates.

The number of subjects considered in the model will be provided by treatment group. P-values of the effects based on the Wald chi-square test will be presented. Treatment effect (colistimethate sodium vs placebo) will be presented as the adjusted hazard ratio with the associated 95% Wald CIs. An adjusted hazard ratio <1 will indicate that colistimethate sodium increases the [redacted] compared to placebo.

To investigate the impact that discontinuations may have on the trial results, a [redacted] analysis will be conducted for the mITT Population. Discontinuers will be counted as failures with their last follow-up date, i.e. date of discontinuation, considered as the time of event.

The main analysis will also be repeated considering the subgroup of mITT subjects who were considered adherent, i.e. had an adherence until the first pulmonary exacerbation of at least 80%.

[redacted] *Analysis for the Effect of Concomitant Antibiotic Therapy*

A supportive analysis examining the impact of antibiotic use (by adding an additional covariate to the Cox proportional hazard regression model so that the hazard ratio is adjusted for this) will be conducted to determine if the use of antibiotics for conditions other than [redacted] has any impact on [redacted].

The list of medications coded to WHO-DD Preferred Terms for antibiotics and anti-pseudomonal antibiotics are included in Appendix 3. If any medication in the list has a related [redacted], the response to the question '[redacted] on the [redacted] page for that [redacted] will then be checked to see whether or not the [redacted] in the opinion of the Investigator. If answered "No", the medication was not taken for a [redacted] and will be included as antibiotics used for conditions other than a [redacted]. Medications in the resulting list that do not have a related [redacted] will also be checked and included as antibiotics used for conditions other than a [redacted].

Two additional tables will be presented:

- Supportive Cox proportional hazards analysis with use of any antibiotics for conditions other than a [redacted] (Yes/No) as an additional covariate.

- Supportive Cox proportional hazards analysis with use of any anti-pseudomonal antibiotics for conditions other than a protocol-defined pulmonary exacerbation (Yes/No) as an additional covariate.

4.7.6.2 [redacted]

For the [redacted] the following weights will be calculated:

- [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

Each domain score will be calculated as follows:

- [redacted]

The total score will be calculated as follows:

- [redacted]

Missing data will be dealt with as described in [redacted]

Weights of each item and other details for calculation are reported in [redacted]

The [redacted] and [redacted] ([redacted]) assessed at Visits 3 - 7 (End of Treatment) will be summarised by treatment group using descriptive statistics including 25th and 75th percentiles. Results for absolute changes from baseline will also be reported. Due to CTP amendments and to the corresponding changes in the procedures schedule, not all the subjects have undergone the same sequence of assessments. All the values collected will be summarised jointly. Considering the presence of a stratified and permutated blocks randomisation list no imbalance between treatments is expected.

Change from baseline in [redacted] total score at Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment-by-visit interaction, use of stable concomitant therapy with oral macrolides and pooled site, i.e. country, as detailed in Section 4.9.1, as fixed effects and baseline value as covariate. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom. The least square means in each treatment group, the least square mean differences between treatments, their 95% CIs and associated p-values overall and at each visit will be estimated by the model. The OBSMARGINS option will be used. A two-sided p-value of <0.05 for the overall mean difference between treatments will be considered statistically significant.

The above summaries/analyses will be performed using the mITT and PP Populations. Results for the PP Population will be considered as supportive.

Notes:

- While for Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7 the 3-month version of the [redacted] is used, for Visit 2 data are collected for the 4-week version. Visit 2 scores will not be included in the linear mixed model analysis but they will be included in the descriptive analysis.

4.7.6.3 [redacted]

Summary statistics of the [redacted] and absolute change from baseline will be provided by treatment group for each trial visit.

Due to CTP amendments and to the corresponding changes in the procedures schedule and due to differences in the schedule of assessments in the local versions of the CTP, not all the subjects have undergone the same sequence of laboratory assessments. All the values collected will be summarised jointly. Considering the presence of a stratified and permutated blocks randomisation list no imbalance between treatments is expected.

The [redacted] as determined by [redacted] (Visit 2) to Day 28 (Visit 3) will be compared between the treatment groups by an ANCOVA model including treatment, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as fixed effects and baseline value as covariate. Least square means in each treatment group, least square mean difference between treatments, their 95% CIs and associated p-value will be estimated. OBSMARGINS option will be used for least square means estimates. A two-sided p-value of <0.05 for the overall mean difference between treatments will be considered statistically significant.

The analysis of covariance model will include only complete cases. [redacted] analysis might be added during the blind review meeting.

The above summaries/analyses will be performed using the mITT Population.

4.7.6.4 [redacted]

A single endpoint of the number and the percentage of subjects with severe [redacted] will be presented. [redacted] [redacted] [redacted] [redacted] documented on the [redacted] form of the eCRF are presumed to include episodes of pneumonia which require intravenous antibiotics and/or hospitalisation. [redacted] form of the eCRF that is linked to an adverse event with a Preferred Term of 'Pneumonia' but does not have any associated intravenous antibiotics or hospitalisation will be assumed to be a [redacted]. Data will be reviewed during the blind review meeting and documented in the Blind Data Review and Analysis Sets Report.

A [redacted] will be defined as treated with systemic antibiotic therapy if a treatment is recorded in the Systemic Antibiotic Therapy form of the eCRF.

The corresponding adjusted mean annual [redacted] rate estimated by a negative binomial model with the same characteristics as the primary efficacy model as detailed in Section 4.7.4 will be analysed. The adjusted mean annual [redacted] in each treatment group and the adjusted rate ratio with their 95% CIs will be estimated by the model. An adjusted rate ratio <1 will indicate that colistimethate sodium decreases the rate of [redacted] compared to placebo. A two-sided Wald chi-square test p-value of <0.05 will be considered statistically significant. P-values of the effects based on Wald chi-square test will also be presented.

The above summary/analysis will be performed using the mITT Population.

4.7.6.5 [redacted]

The time to first severe NCFB pulmonary exacerbation will be analysed and tested using a log-rank test as detailed in Section 4.7.6.1 for the [redacted].

A log-rank sum test will be used to compare the survival distributions of the two treatment groups. A two-sided p-value of <0.05 will be considered statistically significant.

The above summary/analysis will be performed using the mITT Population.

4.7.6.6 [redacted]

The [redacted] will be presented by treatment group.

It will be computed with the following formula:

> [redacted] = (follow-up time [days] – sum of durations of [redacted]) / follow-up time (years).

Follow-up time will be computed as detailed in Section 4.1.7.

For [redacted] [redacted] [redacted] with a resolution date after the treatment completion/discontinuation, the number of days of duration after the treatment completion/discontinuation, i.e. out of the follow-up period, will be subtracted from the sum of durations of [redacted].

Non-parametric ANCOVA model with a randomisation-based methodology as proposed by Koch et al [4] will be used to analyse the ratio of the means between colistimethate sodium and placebo adjusting for any covariates effect and test the null hypothesis of the ratio of means equal to 1. Considering the sample size foreseen for this analysis, there won't be any correction for type I error. A LOGRATIO conversion will be applied.

The model will include treatment group, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as covariates. No stratification variable will be included.

Treatment effect coefficient will be presented along with standard error, associated test statistic and two-sided p-value. A two-sided p-value of <0.05 will be considered statistically significant.

Treatment effect coefficient and associated 95% CI will be exponentiated to obtain estimates and 95% CI for the ratio of the means.

Due to the fact that the p-value computation is based on the re-randomisation of the population, while the CI is based on repeated random sampling theory, there might be disagreement regarding the treatment effect using these two different approaches. Even if these occurrences are quite infrequent, it's worth stating that the p-value from the randomisation test is based on a more realistic and minimal assumptions and should take precedence [5].

As a supportive analysis, the annualised number of [redacted] days will also be compared between the treatment groups using an ANCOVA model including treatment, pooled site, i.e. country, as detailed in Section 4.9.1, and use of stable concomitant therapy with oral macrolides as fixed effects. Least square means in each treatment group, least square mean difference between treatments, their 95% CIs and associated p-value will be estimated. OBSMARGINS option will be used for least square means estimates.

4.7.6.7 [redacted]

Total number of [redacted] and [redacted] will be described overall and by treatment group.

Total number of [redacted] per patient will be computed by summing [redacted] form. Number of [redacted] will be computed considering [redacted]. Namely:

- [redacted]

Where:

- [redacted] = sum {[[redacted] 1, [redacted] 2, etc.] / [redacted]
- [redacted] Assessment i = Coeff i * {(*part1*) [(Date of Assessment i) – (Date of Assessment i-1) + 1]/2 + (*part2*) [(Date of Assessment i+1) – (Date of Assessment i)]/2}

  Where Coeff i = 1 if Employment status equal to Employed or Temporarily Employed at Assessment i, Coeff i = 0 otherwise.

Treatment results will be compared using an independent groups t-test by means of the Satterthwaite method [6]. The corresponding two-sided p-value will be presented. A two-sided p-value of <0.05 will be considered statistically significant. Mean difference, computed as colistimethate sodium - placebo, and corresponding 95% CI will also be presented.

The above summaries/analyses will be performed using the mITT Population.

Notes:

- [redacted] of first and last assessment will include only the subsequent period (referred to in the formula as part 2) and previous period (referred to in the formula as part 1), respectively.
- [redacted] relies on the assumption that no change [redacted] occurs during the [redacted] computed for each assessment.

4.7.6.8 [redacted]

The [redacted] will be provided overall and by treatment group. Percentages will be computed on the total number of subjects with at least one pulmonary exacerbation.

The relative risk of [redacted] for colistimethate sodium/placebo will be provided with 95% asymptotic CIs. Treatment differences will be assessed using a Fisher Exact test. A two-sided p-value of <0.05 will be considered statistically significant.

The number of [redacted] will be summarised presenting summary statistics for continuous variables on subjects with at least one [redacted].

Moreover, tables will present the number and percentages of subjects with at least [redacted] having:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The total duration of [redacted] will be summarised by treatment group using descriptive statistics for continuous variables.

The duration of [redacted] will also be reported for the following categorisations:

- [redacted] days;
- [redacted] days;
- [redacted] days;
- Not Evaluable.

In case of [redacted], the duration of [redacted] will be calculated using the following formula:

- Duration of [redacted] = [redacted] – [redacted]1.

In case of missing [redacted] or [redacted] the [redacted] will be classified as “Not Evaluable”.

The above summaries/analyses will be performed using the mITT Population.

4.7.6.9 [redacted]

For the [redacted] the score for the following domains will be calculated and analysed with a hierarchical approach as per the following order:

- [redacted] Domain: items 1, 2, 3, 4, 16;
- [redacted] Domain: items 17, 20, 25, 27, 28;
- [redacted] Domain: items 6, 8, 9;
- [redacted] Domain: items 7, 10, 11, 23;
- [redacted] Domain: items 18, 19, 22, 26;
- [redacted] Domain: items 12, 13, 14;

- [redacted] Domain: items 5, 15, 21, 24;
- [redacted] Domain: items 29, 30, 31, 32, 33, 34, 35, 36, 37.

Details for calculations are reported in Appendix 2: [redacted] Version 3.0.

The [redacted] domain scores assessed at Visits 3 - 7 (End of Treatment) will be summarised by treatment group using descriptive statistics including 25th and 75th percentiles. Results for absolute changes from baseline will also be reported. Due to CTP amendments and to the corresponding changes in the procedures schedule, not all the subjects have undergone the same sequence of assessments. All the values collected will be summarised jointly. Considering the presence of a stratified and permutated blocks randomisation list no imbalance between treatments is expected.

Change from baseline in each [redacted] domain score will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment-by-visit interaction, use of stable concomitant therapy with oral macrolides and pooled site, i.e. country, as detailed in [redacted], as fixed effects and baseline value as covariate. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom. The least square means in each treatment group, the least square mean differences between treatments, their 95% CIs and associated p-values overall and at each visit will be estimated by the model. The OBSMARGINS option will be used. A two-sided p-value of <0.05 for the overall mean difference between treatments will be considered statistically significant.

The above summaries/analyses will be performed using the mITT Population.

4.8 Safety Analysis

All safety variables will be summarised overall and by treatment group using the Safety Population.

The safety variables are:

- AEs;
- Spirometry results;
- [redacted].
- Vital signs;
- Physical examination results;
- Haematology and clinical chemistry parameters;
- 12-lead ECG parameters.

4.8.1 Adverse Events

An AE is "any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".

An AE will be regarded as treatment-emergent if it has an onset date on or after the date of first IMP dose. For AEs with onset date on day of first IMP dose, the variable “Prior to first IMP administration?” in the Adverse Events eCRF form will be considered. AEs prior to first IMP administration will be considered as non-treatment-emergent. All other AEs, i.e. AEs with negative or missing answers to the question "Prior to first IMP administration?" will be considered as TEAEs. Partially missing dates will be handled as outlined in Section 4.11. If an AE has a partial or fully missing date, and it is unclear whether the AE is treatment-emergent, it will be assumed that it is.

Only TEAEs will be included in the AE and SAE summaries. Non-treatment-emergent events will be included in the subject listings and flagged but not included in the summaries.

A summary table will present the number and percentage of subjects reporting:

- Any TEAEs;
- Any TEAEs by severity;
- Any TEAEs by relationship to IMP;
- Any TEAEs by action taken with IMP;
- Any Serious TEAEs;
- Any Fatal TEAEs.

The number of events occurring will also be reported.

Related AEs are those events for which there is a reasonable possibility that the IMP caused the event. When relationship to IMP is missing for a TEAE it will be imputed to be drug-related. Every effort should be made to query the site for complete data entry prior to database lock.

Fatal AEs are those reported with an outcome of "Fatal".

The number (and percentage) of subjects experiencing at least one TEAE, along with the number of events occurring, will be summarised by MedDRA SOC and PT, overall and by maximum severity.

A subject with more than one occurrence of the same AE in a particular SOC or PT will be counted only once in the total of those experiencing AEs in that particular SOC or PT. Two AEs with the same SOC or PT will be considered as two different events when calculating the "number of events" in the tables.

For summaries by maximum severity, if a subject experiences more than one event in the same SOC and PT, the subject will be counted in the maximum severity but all the events will be reported in their severity level. Maximum severity will be ranked as follows: severe > moderate > mild > unknown.

4.8.1.1 Subsets

- Separate summary tables by SOC and PT will be presented for treatment-emergent SAEs.
- Separate summary tables by SOC and PT and by SOC, PT and maximum severity will be presented for related TEAEs.
- Separate summary tables by SOC and PT will be presented for treatment-emergent related SAEs.

- Separate summary tables by SOC and PT will be presented for treatment-emergent AEs leading to the permanent discontinuation of IMP. An AE leading to discontinuation is an AE with action taken with IMP equal to "Permanently discontinued".
- Separate summary tables by SOC and PT will be presented for treatment-emergent fatal SAEs.
- Treatment-emergent SAEs and fatal AEs will be listed separately.
- The most frequent MedDRA PTs (≥5% of subjects with events in any treatment group) will be presented overall and by treatment. PTs will be used for tabulation, sorted by decreasing overall frequency.

All other information collected will be listed, as appropriate. Additionally, listings will display relative day of AE onset.

The relative day of AE onset will be calculated as follows:

- For pre-treatment AEs:
  - AE onset date - date of first IMP dose (if AE onset date is completely known);
  - missing (if AE onset date is incomplete or unknown).
- For TEAEs:
  - AE onset date - date of first IMP dose +1 (if AE onset date is completely known);
  - missing (if AE onset date is incomplete or unknown).

Notes:

- AEs will be coded using MedDRA version 19.1 or higher (please refer to the final Data Management Plan for the latest coding information).
- Terms will be displayed in descending overall frequency (and then alphabetically) of SOCs and in descending overall frequency (and then alphabetically) of PTs within each SOC.

4.8.2 Spirometry Results

The following spirometry parameters will be summarised for each visit, as applicable, by treatment group and overall:

- FEV_1 (L);
- Predicted FEV_1 (%);
- FVC (L);
- Predicted FVC (%);
- Change in FEV_1 (L) from pre-salbutamol/albuterol intake to 30 minutes post-IMP.

Absolute value and change from baseline at each visit will be described by means of summary statistics for continuous variables.

The number and percentages (along with exact 95% CIs) of subjects experiencing bronchospasm at Visit 7 (End of Treatment) following IMP administration as clinically (as collected in the Spirometry eCRF forms) or spirometrically (>15% decrease in FEV_1 from pre-salbutamol/albuterol intake to 30 minutes post-IMP) determined will be summarised by treatment. The number of subjects experiencing bronchospasm at all other visits will be listed. The subject will be considered spirometrically to have had a bronchospasm if presenting >15% decrease in FEV_1 from pre-salbutamol/albuterol intake to 30 minutes post-IMP or a positive answer to the above question.

The relative risk for colistimethate sodium/placebo will be provided with 95% asymptotic CIs. Treatment differences will be assessed using a Fisher Exact test. Subjects with no available result will be excluded from the analysis.

Notes:

- Change in FEV_1 (L) will be calculated as FEV_1 30 minutes post-IMP – FEV_1 pre-salbutamol/albuterol intake;
- Percentage change in FEV_1 (%) will be calculated as 100*(change in FEV_1 [L] / FEV_1 pre-salbutamol/albuterol intake).

4.8.3 [redacted] to Colistimethate Sodium

The number and percentage of subjects whose [redacted] (i.e. [redacted]", as per data received from Eurofins central laboratory) [redacted] at the end of treatment (at 12 months [Visit 7]) will be presented overall and by treatment. Results will be presented along with number and percentage of subjects with result to susceptibility testing equal to [redacted], "Moderate" and "NA".

The summary will be repeated by status of previous usage of colistimethate sodium/colistin as detailed in Section 4.1.5.

Missing data will not be imputed. A separate summary will be presented summarising the last available results for each subject.

Notes:

- Based on data collected on the Non-CF Bronchiectasis History eCRF form regarding previous usage of colistimethate sodium/colistin, subjects will be classified into:
    - Without any previous usage of colistimethate sodium/colistin;
    - With previous usage of colistimethate sodium/colistin;
    - With missing data regarding previous usage of colistimethate sodium/colistin.

4.8.4 Haematology, Clinical Chemistry and Renal Function Parameters

The following haematology and clinical chemistry (including renal function) parameters will be summarised.

Category	**Parameter**	**Unit**
Haematology	Haemoglobin	g/L
	Haematocrit	L/L
	Red Cell Count	x10E12/L
	White Cell Count	x10E9/L
	Neutrophils	%
	Total Lymphocytes	%
	Monocytes	%
	Eosinophils	%
	Basophils	%
	Neutrophils (Abs)	x10E9/L
	Total Lymphs (Abs)	x10E9/L
	Monocytes (Abs)	x10E9/L
	Eosinophils (Abs)	x10E9/L
	Basophils (Abs)	x10E9/L
	Platelets	x10E9/L
Chemistry	Sodium	mmol/L
	Potassium	mmol/L
	Chloride	mmol/L
	Uric Acid	mmol/L
	Bilirubin (Total)	umol/L
	Bilirubin (Conj)	umol/L
	AST	U/L
	ALT	U/L
	GGT	U/L
	ALP (Alk Phos)	U/L
	Calcium	mmol/L
	Amylase	U/L
Renal Function	BUN (Urea)	mmol/L
	Creatinine	umol/L

Results as assessed at each applicable visit will be summarised by treatment group and overall using descriptive statistics for continuous variables. Absolute and percentage changes from baseline will also be presented.

A shift table will also be provided presenting results as lower than, within and higher than the central laboratory normal range. This will show the shift from baseline to each post-baseline visit, as well as to the most extreme value (defined as the value furthest outside [below or above] the central laboratory normal range) at any visit after baseline, including unscheduled visits.

Notes:

- Change from baseline for each parameter will be computed using the formula:

  Change (unit) = (AVAL [unit] - baseline AVAL [unit]);

- All results outside the central laboratory normal range will be flagged in the data listings;

- Repeat laboratory results within a visit will replace the original value;

- Due to CTP amendments and to the corresponding changes in the procedures schedule and due to differences in the schedule of assessments in the local versions of the CTP, not all the subjects have undergone the same sequence of laboratory assessments. All the values collected will be summarised jointly. Considering the presence of a stratified and permutated blocks randomisation list, no imbalance between treatments is expected.

4.8.5 Vital Signs

Respiratory rate (breaths per minute), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg) and body temperature (°C) will be summarised overall and by treatment group at each applicable visit by means of descriptive statistics. Absolute and percentage changes from baseline to each visit after the first IMP dose will also be summarised. The number and percentage of subjects with Normal, Abnormal NCS and Abnormal CS results will be presented.

A shift table will also be provided for the clinical assessment. This will show the shift from baseline to each post-baseline visit, as well as to the worst overall result assessed at any visit after baseline, including unscheduled visits.

Additionally, for the Visit 7 summary, statistics for weight (kg) and BMI (kg/m^2) will be presented.

Notes:

- BMI will be computed as weight at Visit 7 (kg) / (height at Visit 1 [m^2]);

- Change from baseline for each parameter will be computed using the formula:

  Change (unit) = AVAL (unit) - baseline AVAL (unit);

- Due to CTP amendments and to the corresponding changes in the procedures schedule and due to differences in the schedule of assessments in the local versions of the CTP, not all the subjects have undergone the same sequence of vital sign assessments. All the values collected will be summarised jointly. Considering the presence of a stratified and permutated blocks randomisation, list no imbalance between treatments is expected.

4.8.6 Physical Examination Results

Physical Examination findings collected at each visit will be described by treatment group and overall presenting the number and percentage of subjects with Normal, Abnormal NCS and Abnormal CS results for each body system as per the eCRF. Results for other body systems collected, but not specified in the eCRF will be listed only.

A shift table will also be provided. This will show the shift from baseline to each post-baseline visit, as well as to the worst overall result assessed at any visit after baseline, including unscheduled visits.

Notes:

- Due to CTP amendments and to the corresponding changes in the procedures schedule and due to differences in the schedule of assessments in the local versions of the CTP, not all the subjects have undergone the same sequence of physical examinations. All the values collected will be summarised jointly. Considering the presence of a stratified and permutated blocks randomisation list, no unbalance between treatments is expected.

4.8.7 12-Lead ECG

The 12-lead ECG overall interpretation at Visit 1 and Visit 7 will be described by treatment group and overall presenting the number and percentage of subjects with Normal, Abnormal NCS and Abnormal CS results. A shift table will also be provided showing the change from baseline to Visit 7, as well as to the worst overall result assessed at any visit after baseline, including unscheduled visits.

4.8.8 Pregnancy Test

Results from dipstick urine pregnancy tests for women of child-bearing potential will be listed only.

4.8.9 Other Data

All other data collected in the eCRF will be listed only.

4.9 Adjustment for Covariates

The adjusted mean annual NCFB pulmonary exacerbation rate will be estimated by a negative binomial model including treatment, use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin: Yes/No) and pooled site, i.e. country, as detailed in Section 4.9.1, as fixed effects and log-time on treatment as an offset. An exploratory model will also be fitted considering the number of NCFB pulmonary exacerbations requiring oral/intravenous antibiotics in the last 12 months prior to study entry. The non-parametric ANCOVA model on ordered score for number of pulmonary exacerbations and on the annualised number of pulmonary [redacted] will include the same covariates.

The Cox proportional hazard regression model for [redacted] will include use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin: Yes/No) and pooled site, i.e. country, as covariates.

In the analysis of [redacted] total score and [redacted] domain scores, a linear mixed model for repeated measures will be applied. This will include treatment, visit, treatment-by-visit interaction, use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin: Yes/No) and pooled site, i.e. country, as fixed effects and baseline value as covariate.

The [redacted] will be analysed by means of an ANCOVA model including treatment, pooled site, i.e. country, and use of stable concomitant therapy with oral macrolides (azithromycin or erythromycin or clarithromycin: Yes/No) as fixed effects and baseline value as covariate.

4.9.1 Site Effects

Sites will be pooled into clusters to fit the model in order to avoid estimation issues for too many degrees of freedom and levels with too low numbers of subjects included, considering that the estimated number of sites participating in the trial is approximately 80, the enrolment is competitive, and the total number of randomised subjects is approximately 420.

Given the similarity in geographic characteristics and concomitant treatments used (other than oral macrolides: i.e. bronchodilators, corticosteroids, etc) sites will be pooled into their corresponding countries.

Any change from this strategy will be discussed at the blind review meeting and documented in the Blind Data Review and Analysis Sets Report. In any case, pooling of the sites will not be data-dependent. The choice will be made based on medical consideration about the sites involved in the study.

4.10 Protocol Deviations

4.10.1 Major Protocol Deviation Criteria

Exact definitions of major protocol deviations affecting safety and efficacy analyses will be discussed at the blind review meeting and documented in the Blind Data Review and Analysis Sets Report. The Protocol Deviation and Non-Compliance Management Plan documents the process for identifying protocol deviations that would potentially exclude subjects from the PP Population.

If major protocol deviations occur as outlined in the criteria below, then the data from complete individual subjects, individual visits or individual evaluations will be excluded from the population of analysis as indicated.

Exclusion of subjects or observations from the analyses will be decided jointly by the CRO and Sponsor's Study Team prior to unblinding of the randomisation code and database release.

The subjects or observations to be excluded, and the reasons for their exclusion, will be documented and approved by the above-mentioned persons prior to database release. The documentation will be filed together with the remaining trial documentation.

The number of subjects in each analysis population will be reported. Major protocol deviations excluding subjects from any particular population will be described, reporting the number of protocol violators for each criterion. All major protocol deviations will be listed and summarised for all screened subjects.

Major protocol deviations will be classified according to the following categories:

- Concomitant Medication / Administration of Prohibited Medication;
- Inclusion or Exclusion Criteria;
- Informed Consent / ICF not signed or signed late;
- Informed Consent / Other;

- Investigational Product / Incorrect IMP kit given to subject;
- Investigational Product / IMP Dosing;
- Investigational Product / IMP Storage;
- Investigational Product / Other;
- Met Withdrawal Criteria but was not Withdrawn;
- Patient Privacy (PP) / PP not signed;
- Patient Privacy / Other;
- Randomization / Mis-stratification;
- Randomization / Multiple Randomizations;
- Randomization / Other;
- Randomization / Randomized Not Treated;
- Randomization / Treated and Not Randomized;
- SAE not reported or reported late;
- Study Procedure / Missed procedure;
- Study Procedure / Other;
- Study Procedure / Site Staff Authorization, Delegation, Training;
- Study Procedure / Subject compliance;
- Study Procedure / Unmasking (not per protocol);
- Study Procedure / Visit Missing;
- Study Procedure / Washout;
- Visit Window.

These categories may be amended or other categories may be added, but any changes will be made prior to database lock and will be documented in the Blind Data Review and Analysis Sets Report.

4.10.2 Protocol Deviations

Deviations from the protocol will be documented on an ongoing basis by the study monitors and clinical research associates or designee throughout the study period as detailed in the Protocol Deviation and Non-Compliance Management Plan.

At the time of database lock, prior to unblinding, the project manager or designee will forward all relevant documentation highlighting protocol deviations to the study statistician. These will be listed in the CTR. The study statistician will also verify occurrence of deviations from the protocol checking eCRF data, where feasible.

4.11 Missing Values – Missing Visits

The validity of the negative binomial model planned for the primary efficacy analysis of the mean annual NCFB exacerbation rate relies on the MAR assumption.

The validity of the log-rank test planned for the [redacted] and the supportive Cox proportional hazard regression model relies on the uninformative censoring assumption.

[redacted] analyses will be conducted to investigate the robustness of the conclusions of these analyses. A detailed description of these analyses is provided in Sections 4.7.4.2 and 4.7.6.1.

In the analysis of [redacted] total score and [redacted] domain scores, linear mixed models for repeated measures will be used to handle missing data. Under the MAR assumption, these models provide an unbiased estimate of the treatment effect that would have been observed if all subjects had continued on treatment [7].

The analysis of covariance model for the [redacted] will include only complete cases. [redacted] analyses might be added during the blind review meeting if the amount of missing data makes it reasonable for further investigations of their influence on the overall study results. Decisions will be documented in the Blind Data Review and Analysis Sets Report.

Unless stated otherwise, there will be no imputation of missing values and only observed data will be included in the summaries.

The number of subjects with missing data will be presented under a "Missing" category. Unless otherwise stated, missing values will be included in the denominator count when computing percentages.

When continuous data are being summarised, only the non-missing values will be evaluated for computing summary statistics.

In order to calculate the duration of last usage of colistimethate sodium/colistin and the time from last administration of colistimethate sodium/colistin, the following rules will be applied for partial dates of start and stop date of last administration of colistimethate sodium/colistin:

For the start date:

- if only the day is missing, the first day of the month will be assumed;
- if the day and the month are missing, then the date will not be imputed and the time/duration will be classified as "Not Evaluable".

For the stop date:

- if only the day is missing, the last day of the month will be assumed;
- if the day and the month are missing, then the date will not be imputed and the time/duration will be classified as "Not Evaluable".

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

In case of a partial onset date of a NCFB pulmonary exacerbation due to missing day, the onset of the event will be assumed as the first day of the month. If the resultant derived date is prior to the date of first IMP dose, then it will be assumed to be equal to the first IMP dose date.

In case of a partial resolution date of a NCFB pulmonary exacerbation due to missing day, the resolution of the event will be assumed as the last day of the month. If the resultant derived date is after the treatment completion/discontinuation date, then it will be assumed to be equal to the treatment completion/discontinuation date.

In case a NCFB pulmonary exacerbation presents a symptom with missing duration, following a conservative approach, the longest duration will be imputed.

In order to calculate the duration of each course of systemic antibiotic therapy, the following rules will be applied for partial dates of start and stop date of systemic antibiotic therapies:

For the start date:

- if only the day is missing, the first day of the month will be assumed. If the resulting derived date is prior to the start date of the exacerbation, then start date of therapy will be assumed to be equal to the start date of the exacerbation.
- if the day and the month are missing, then the date will not be imputed.

For the stop date:

- if only the day is missing, the last day of the month will be assumed.
- if the day and the month are missing, then the date will not be imputed and the duration will be classified as "Not Evaluable".

The domain scores of the [redacted] will be considered non-missing if the following conditions are satisfied:

- Symptoms score: missing items ≤ 2;
- Activity score: missing items ≤ 4;
- Impacts score: missing items ≤ 6.

If at least one domain score is missing, the total score will be considered as missing.

The domain scores of [redacted] will be considered non-missing if the responses are missing for half or less of the items in the domain.

If an AE has a partially or fully missing date, and it is unclear whether the AE is treatment-emergent, it will be assumed that it is. In the AEs analysis, when relationship to IMP is missing for a TEAE it will be imputed to be drug-related. Every effort should be made to query the site for complete data entry prior to database lock.

Other critical missing data, if any, will be discussed during the blind review of the data. Decisions will be fully documented in the Analysis Set Specifications Document.

4.12 Deviations from the SAP

Any deviations from the original SAP will be described and justified in the final CTR, whether written post interim or final analysis.

4.13 Changes in Conduct or Planned Analyses from the Protocol

Sections 2.2, 4.4.11, 4.7.5 and 4.7.6.3: The protocol incorrectly referred to the units for the determination of [redacted] which have been reported as [redacted] by the central laboratory.

Section 3.9: The rationale and results for a reassessment of the original sample size calculation are provided to explain the reduced target sample size and associated levels of power.

Section 4.7.4: The protocol states that the Negative Binomial Model will consider the log-time on study as offset. However, as specified in Section 4.1.7, NCFB Pulmonary Exacerbations analyses focus on the treatment period so log-time on treatment will be considered.

Section 4.7.6.1: The protocol states that [redacted] = [redacted]. For time-to-event endpoints, generally the + 1 is not included because this overestimates the time by 1 day for every event, therefore "+ 1" has been deleted.

Section 4.7.6.4: The protocol states that any episodes of pneumonia will be considered as severe pulmonary exacerbations. Any reported episodes of pneumonia which do not require intravenous antibiotics and/or hospitalisation will be data queried to amend the Preferred Term. However, any pulmonary exacerbation on the Pulmonary Exacerbation form of the eCRF that is linked to an adverse event with a Preferred Term of 'Pneumonia' but does not have any [redacted] or [redacted] will be assumed to be a severe NCFB pulmonary exacerbation.

Section 4.7.6.5: The protocol states that the [redacted] total score will be computed and analysed. However, as recommended in the Manual Scoring Instructions[redacted] only the [redacted] domain scores will be presented and analysed.

There have been no other changes in analyses from those defined in the protocol.

4.14 Algorithms/SAS Codes

The SAS codes for descriptive statistics and frequency counts detailed below are examples only and other procedures may be used, if appropriate.

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 ...varn;
    BY byvar; (optional)
    OUTPUT OUT= outset
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std *Q1=q1
Q3=q3; *Include Q1 and Q3 for [redacted] data only;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2 /out= outset;
RUN;
```

- **Tables that need T-Test;**

```
PROC TTEST DATA=dset;
CLASS var1;
VAR var1N;
RUN;
```

- **Tables that need exact 95% CIs for risk difference between groups for proportions and Fisher's Exact:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var*treatment / MEASURES RISKDIFF EXACT ALPHA=0.05;
    EXACT MEASURES;
    OUTPUT OUT= outset EXACT MEASURES RISKDIFF;
WHERE wherever; (optional)
RUN;
```

- **Tables that need 95% CIs within group for binomial proportions:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var1;
    EXACT BINOMIAL;
    OUTPUT OUT= outset BINOMIAL;
RUN;
```

- **Tables that require analysis of (co)variance and 95% CIs between arms for continuous variables:**

```
PROC GLM DATA= dset OUTSTAT=outset;
    CLASS treatment psite med;
```

```
    MODEL change = treatment psite med baseline/ SOLUTION;
    LSMEANS treatment / STDERR PDIFF CL OBSMARGINS;
    BY byvar; (optional)
    WHERE wherever; (optional)
RUN;
```

Notes:

- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);
- Change represents the change from baseline of the variable;
- Baseline represents the baseline value of the variable;
- Treatment order: 1= Colistimethate Sodium, 2= Placebo.

- **Tables that require Kaplan-Meier estimates and log-rank test:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM timelist=(0 28 90 180
270 EoT) reduceout;
     TIME time*event (1);
    ID subject;
    STRATA treatment;
    WHERE wherever; (optional)
RUN;
```

Notes:

- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (1 = censored);
- EoT should be replaced by the last time (in days) to event >270 days (if any);

- **Tables that require Cox proportional hazards model and 95% CIs of hazard ratios between treatments:**

```
PROC PHREG data=dset;
     CLASS treatment psite med;
     MODEL time*event(1) = treatment psite med / ties=exact;
    HAZARDRATIO 'Col. Sodium vs Placebo' treatment / cl=both;
    BY byvar; (optional)
    WHERE wherever; (optional)
RUN;
```

Notes:

- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);
- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (1 = censored);
- If the option ties=exact requires a considerable amount of computer resources, the Efron approximation will be used (*ties=efron*).
- Treatment order: 1= Colistimethate Sodium, 2= Placebo.

- **Tables that require negative binomial modelling, including 95% CIs of treatment ratios:**

```
PROC GENMOD data = dset;
    CLASS treatment psite med;
    MODEL count = treatment psite med / offset=log_years link=log dist=negbin wald
    type3;
    ESTIMATE 'Col. Sodium / Placebo' treatment 1 -1 / exp;
    lsmeans treatment / ilink cl diff exp om;
    BY byvar; (optional)
    WHERE wherever; (optional)
RUN;
```

Notes:

- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);
- Count represents the total number of exacerbations for each patient;
- log_years represents the logarithm of the follow-up time in years;
- Treatment order: 1= Colistimethate Sodium, 2= Placebo.

- **Tables that require linear mixed model for repeated measures and 95% CIs of differences between treatments:**

```
PROC MIXED data = dset;
    CLASS treatment visit psite med sub;
    MODEL change = treatment visit treatment*visit psite med baseline/ s ddfm=kr;
    REPEATED visit / subject=sub type=un r;
    LSMEANS treatment treatment*visit / om at means cl slice=visit;
    LSMESTIMATE treatment
        'Col. Sodium / Placebo'    1 -1 / cl;
    LSMESTIMATE treatment*visit
        'Col. Sodium / Placebo: Visit 4'   1 0 0 0 -1 0 0 0,
        'Col. Sodium / Placebo: Visit 5'   0 1 0 0 0 -1 0 0,
        'Col. Sodium / Placebo: Visit 6'   0 0 1 0 0 0 -1 0,
        'Col. Sodium / Placebo: Visit 7'   0 0 0 1 0 0 0 -1/ cl;
    BY byvar; (optional)
    WHERE wherever; (optional)
RUN;
```

Notes:

- Visit represents the clinic visit;
- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);
- Sub represents the Subject Number;
- Change represents the change from baseline to each visit of the variable;
- Baseline represents the baseline value of the variable;
- Treatment order: 1= Colistimethate Sodium, 2= Placebo.

–

- **Tables that require Prentice, Williams and Peterson Total Time model and 95% CIs of hazard ratios between treatments:**

```
PROC PHREG data=dset;
     CLASS treatment psite med;
     MODEL (tstart , tstop)*status(1) = treatment psite med / ties=Breslow;
     STRATA episode;
    HAZARDRATIO 'Col. Sodium vs Placebo' treatment / cl=both;
    BY byvar; (optional)
    WHERE wherever; (optional)
RUN;
```

Notes:

- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);
- Status represents the censoring indicator (1 = censored);
- Treatment order: 1= Colistimethate Sodium, 2= Placebo;
- Dataset for the analysis should be adequately created: Subjects with no events have a single observation, while subjects with one event have two rows etc… A pair of variables (tstart, tstop) is used to define the time interval of risk. The start time (tstart) is generally equal to 0 for the first event and equals to the last recurrence stop time for further events. During an episode of pulmonary exacerbation, the subejcts can't have another episode. Therefore, they are by definition not at risk for a next event during a previous episode. The stop time (tstop) is a recurrent event time (status = 1) or a censored time (status = 0). The event order should be denoted by variable episode.

- **Multiple Imputation for pulmonary exacerbation rate**

An example of SAS code is provided below for the [redacted] analyses pulmonary exacerbation rate.

<u>Missing at random and copy reference imputation</u>

```
PROC GENMOD DATA=dataset1;
    MODEL count = treatment_d psite_d1-psite_dx med_d / OFFSET=log_years
    DIST=NEGBIN;
    /* >1000 imputations since some will be discarded due to convergence issues with the
    model */
    BAYES NBI=1000 NMC=11000 THIN=10 OUTPOST=dataset2 SEED=34783129;
RUN;

DATA dataset3;
    SET dataset2;
    RENAME treatment_d =c_treatment_d
                psite_d1-psite_dx=c_psite_d1-c_psite_dx
                med_d=c_med_d;
RUN;
```

```
PROC SQL;
    CREATE TABLE dataset4 AS
    SELECT dataset1.*, dataset3.*
    FROM dataset1, dataset3
    ORDER BY Iteration;
QUIT;

DATA dataset5;
    SET dataset4;
    BY Iteration;
    ARRAY c[*] c_psite_d1-c_psite_dx c_med_d;
    ARRAY x[*] psite_d1-psite_dx med_d;
    k=1/Dispersion;
    imp_subj=(years<365/365.25);
    years_imp=MAX(years,365/365.25);
    log_years_imp=LOG(years_imp);
    linpred_1=.;
    IF imp_subj THEN DO;
       years_miss=years_imp-years;
       linpred_1=Intercept;
       DO i=1 TO DIM(c);
           linpred_1+c[i]*x[i];
       END;
       linpred_mar=linpred_1+c_treatment_d*treatment_d;
       linpred_cr=linpred_1+c_treatment_d;
       y1hat_mar=years*EXP(linpred_mar);
       y2hat_mar=years_miss*EXP(linpred_mar);
       y1hat_cr=years*EXP(linpred_cr);
       y2hat_cr=years_miss*EXP(linpred_cr);
       CALL STREAMINIT(3231212);
       y2_mar=RAND('NEGBINOMIAL',(1+y1hat_mar)/(1+y1hat_mar+y2hat_mar),k+cou
    nt);
       y2_cr=RAND('NEGBINOMIAL',(1+y1hat_cr)/(1+y1hat_cr+y2hat_cr),k+count);
       y_imp_mar=count+y2_mar;
       y_imp_cr=count+y2_cr;
    END;
    ELSE DO;
       y_imp_mar=count;
       y_imp_cr=count;
    END;
RUN;
```

Notes:

- dataset1 includes one record per patient;
- count represents the total number of exacerbations observed for each patient;
- treatment represents the treatment group (treatment order: 1 = colistimethate sodium, 2 = placebo);

- treatment_d represent the dummy variables for treatment group (values of the dummy variables: 0 for colistimethate sodium; 1 for placebo);
- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- psite_d1-psite_dx represent the dummy variables for the (pooled) site;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);
- med_d represents the dummy variable for use of stable concomitant therapy with oral macrolides;
- years represents the follow-up time in years;
- log_years represents the logarithm of the follow-up time in years.

<u>Analysis step</u>

The imputed dataset obtained using the above SAS code will be finally analysed and the results will be combined.

```
ODS OUTPUT LSMeans=lsmeans1 Estimates=ratios1;
PROC GENMOD DATA=dataset5;
    BY Iteration;
    CLASS treatment psite med;
    /* MAR imputation */
    MODEL y_imp_mar = treatment psite med/ OFFSET=log_years_imp DIST=NEGBIN;
    /* Alternative MODEL statement: copy reference imputation */
    MODEL y_imp_cr = treatment psite med/ OFFSET=log_years_imp DIST=NEGBIN;
   LSMEANS treatment / ilink cl diff exp om;
       ESTIMATE 'Col. Sodium / Placebo' treatment 1 -1 / exp;
RUN;

DATA lsmeans2;
    SET lsmeans1 (WHERE=(zValue ne .));
    BY Iteration;
    IF first.Iteration THEN _Imputation_+1;
    IF _Imputation_ LE 1000;
RUN;

ODS OUTPUT ParameterEstimates=lsmeans3;
PROC MIANALYZE PARMS=lsmeans2;
    CLASS treatment;
    MODELEFFECTS treatment;
RUN;

DATA lsmeans4;
    SET lsmeans3;
    exp_est=EXP(Estimate);
    exp_lcl=EXP(LCLMean);
    exp_ucl=EXP(UCLMean);
RUN;
```

```
DATA ratios2 (RENAME=LBetaEstimate=Estimate);
    SET ratios1 (WHERE=(ChiSq ne .));
    BY Iteration;
    IF first.Iteration THEN _Imputation_+1;
    IF _Imputation_ LE 1000;
    Effect='Label';
RUN;

ODS OUTPUT ParameterEstimates=ratios3;
PROC MIANALYZE PARMS =ratios2;
    CLASS Label;
    MODELEFFECTS Label;
RUN;

DATA ratios4;
    SET ratios3;
    exp_est=EXP(Estimate);
    exp_lcl= EXP (LCLMean);
    exp_ucl= EXP (UCLMean);
RUN;
```

- **Tables that require Non-Parametric Randomization-Based Analysis of Covariance.**

  The macro NParCov4, reported in Appendix 4, will be applied with the following parameters.

  For the analysis of pulmonary exacerbation score:

```
%NPARCOV4( outcomes = outcome,
             covars = psite med,
            trtgrps = treatment,
             strata = NONE,

             hypoth = NULL /*for p-value*/,
             hypoth = ALT  /*for CI*/,

          transform = NONE,

              dsnin = dataset,
             dsnout = outdat,
              exact = %str(NO)
         );
```

  For the analysis of annualised number of pulmonary [redacted]

```
%NPARCOV4( outcomes = outcome,
             covars = psite med,
            trtgrps = treatment,
             strata = NONE,
```

```
                    hypoth = NULL /*for p-value*/,
                    hypoth = ALT  /*for CI*/,

                 transform = LOGRATIO,

                     dsnin = dataset,
                    dsnout = outdat,
                     exact = %str(NO)
                );
```

Notes:

- dataset includes one record per patient;
- outcome represents the outcome observed for each patient, ie the pulmonary exacerbation score or the annualised number of pulmonary [redacted]
- treatment represents the treatment group (treatment order: 1 = colistimethate sodium, 0 = placebo);
- Psite represents the pooled site, i.e. country, as detailed in Section 4.9.1;
- Med represents use of stable concomitant therapy with oral macrolides (e.g. azithromycin or erythromycin or clarithromycin) (Yes/No);

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.4 or a later version.

- All TFLs will be produced in landscape format on *American letter size / A4 paper size*, unless otherwise specified. *<Check with Medical Writer the CSR paper size so both documents are consistent>*
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no colour).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C$_{max}$) may be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

Headers

- All output should have the following header at the top left of each page:

Zambon Protocol Z7224L01 [redacted] study number [redacted])

- All output should specify the Draft/Final Run status at the top centre of each page.
- All output should have Page n of N at the top right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

Display Titles

- Each output is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents. All titles will be centre-aligned. The analysis population will be identified on the line immediately following the title. The output number and title will be single-line spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed

(mITT Population)

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified, frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place. Percentages between 0.05% and 0.1% will be rounded to 0.1%. Percentages less than 0.05% will be displayed as <0.1%. Percentages between 99.90% and 99.95% will be rounded to 99.9%. Percentages more than 99.95% will be displayed as >99.9%.

P-values, if applicable, will be presented to 5 decimal places. If the p-value is less than 0.00001 then it will be presented as <0.00001. If the rounded result is a value of 1.00000, it will be displayed as >0.99999.

Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion.

Unless otherwise specified, listings should be sorted by treatment group, subject and visit and have the source ADaM dataset referenced in a footnote.

All tables, listings and figures will be converted into Rich text format with the format/file extension specified and collated into three separate complete documents. The combined documents will be in .pdf format.

5.3 Tables

5.3.1 Section 14.1: Demographic and Baseline

5.3.2 Section 14.2: Primary

Table 14.2.1.1.2	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model	(PP Population)
Table 14.2.1.1.3	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - Alternative Definition of Pulmonary Exacerbation	(mITT Population)
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Table 14.2.1.1.5	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - Adherent Subjects	(mITT Population)
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5.3.3 Section 14.2: Secondary

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Table 14.2.2.1.2	[redacted]: Kaplan-Meier Estimates	(PP Population)
Table 14.2.2.2.1	[redacted]: Cox proportional hazard regression model	(mITT Population)
Table 14.2.2.2.2	[redacted]: Cox proportional hazard regression model	(PP Population)
Table 14.2.2.2.3	[redacted]: Cox proportional hazard regression model - [redacted] Analysis for the Effect of Concomitant Antibiotic Therapy	(mITT Population)
Table 14.2.2.2.4	[redacted]: Cox proportional hazard regression model - [redacted] Analysis for the Effect of Concomitant Anti-Pseudomonal Antibiotic Therapy	(mITT Population)

Table 14.2.2.3	[redacted]: Kaplan-Meier Estimates - [redacted] Analysis for Discontinuers	(mITT Population)
Table 14.2.2.4	[redacted]: Kaplan-Meier Estimates - Adherent Subjects	(mITT Population)
Table 14.2.2.5.1	[redacted] Domain Scores and Total Score Results and Change Versus Baseline	(mITT Population)
Table 14.2.2.5.2	[redacted] Domain Scores and Total Score Results and Change Versus Baseline	(PP Population)
Table 14.2.2.5.3	[redacted] Linear Mixed Model for Repeated Measures for Change from Baseline in Total Score	(mITT Population)
Table 14.2.2.5.4	[redacted] Linear Mixed Model for Repeated Measures for Change from Baseline in Total Score	(PP Population)
Table 14.2.2.6.1	[redacted]: Results and Change from Baseline	(mITT Population)
Table 14.2.2.6.2	[redacted]: ANCOVA Model for Change from Baseline at Visit 3	(mITT Population)
Table 14.2.2.7.1	[redacted]: Mean Annual Rate by Negative Binomial Model	(mITT Population)
Table 14.2.2.7.2	[redacted]: Kaplan-Meier Estimates	(mITT Population)
Table 14.2.2.8.1	[redacted]: Non-Parametric ANCOVA model	(mITT Population)
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Table 14.2.2.9	[redacted]	(mITT Population)
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Please Note: Section 14.3.3 (Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events) is not to be used for any tables

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5.5 Figures

Figure 14.2.2.1.3	Kaplan-Meier Curve for CCI	(mITT Population)
Figure 14.2.2.1.4	Kaplan-Meier Curve for CCI	(PP Population)

Tables, Listings, and Figures will follow the format of: Zambon-Z7224L01-SAP-Shells-FINAL-v1.0-dd-Mmm-yyyy; where dd-Mmm-yyyy denotes the date of the Final v1.0 shells document.

5.6 References

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4 Koch, G. G., Tangen, C. M., Jung, J. and Amara, I. A. (1998), Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non- parametric strategies for addressing them. Statist. Med., 17: 1863-1892. doi:10.1002/(SICI)1097-0258(19980815/30)17:15/16<1863::AID-SIM989>3.0.CO;2-M

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[redacted] Quality of Life questionnaire - Bronchiectasis manual. Previously available from: http://www.psy.miami.edu/qol_b/scoring.phtml

[redacted] Jones P. St George's Respiratory Questionnaire Manual, Version 2.3. Division of Cardiac and Vascular Science, St George's, University of London.

10 Quanjer et al., Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur Respir J. 2012 Dec 40(6):1324-43.

Appendix 1: CCI

[redacted] CCI. Below weights for each item and other details for calculation are reported.

Please tick in one box to show how you describe your current health (not used in total or domain score calculations):

Response
Very good ☐
Good ☐
Fair ☐
Poor ☐
Very poor ☐

ITEM WEIGHTS

PART 1

1) Over the past 4 weeks / 3 months, I have coughed:

Response	Weight
Most days a week	80.6
Several days a week	63.2
A few days a month	29.3
Only with chest infections	28.1
Not at all	0.0

2) Over the past 4 weeks / 3 months, I have brought up phlegm (sputum):

Response	Weight
Most days a week	76.8
Several days a week	60.0
A few days a month	34.0
Only with chest infections	30.2
Not at all	0.0

3) Over the past 4 weeks / 3 months, I have had shortness of breath:

Response	Weight
Most days a week	87.2
Several days a week	71.4
A few days a month	43.7
Only with chest infections	35.7
Not at all	0.0

4) Over the past 4 weeks / 3 months, I have had attacks of wheezing:

Response	Weight

Most days a week	86.2
Several days a week	71.0
A few days a month	45.6
Only with chest infections	36.4
Not at all	0.0

5) During the past 4 weeks / 3 months, how many severe or very unpleasant attacks of chest trouble have you had?

Response	Weight
More than three attacks	86.7
3 attacks	73.5
2 attacks	60.3
1 attack	44.2
No attacks	0.0

6) How long did the worst attack of chest trouble last?

Response	Weight
A week or more	89.7
3 or more days	73.5
1 or 2 days	58.8
Less than a day	41.9

7) Over the past 4 weeks / 3 months, in an average week, how many good days (with little chest trouble) have you had?

Response	Weight
No good days	93.3
1 or 2 good days	76.6
3 or 4 good days	61.5
Nearly every day is good	15.4
Every day is good	0.0

8) If you have a wheeze, is it worse in the morning?

Response	Weight
No	0.0
Yes	62.0

PART 2

Section 1

How would you describe your chest condition?

Response	Weight
The most important problem I have	83.2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0.0

If you have ever had paid employment.

Response	Weight
My chest trouble made me stop work altogether	88.9
My chest trouble interferes with my work or made me change my work	77.6
My chest trouble does not affect my work	0.0

Section 2

Questions about what activities usually make you feel breathless these days.

Response	Weight
Sitting or lying still	90.6
Getting washed or dressed	82.8
Walking around the home	80.2
Walking outside on the level	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1
Playing sports or games	72.1

Section 3

Some more questions about your cough and breathlessness these days.

Response	Weight
My cough hurts	81.1
My cough makes me tired	79.1
I am breathless when I talk	84.5
I am breathless when I bend over	76.8
My cough or breathing disturbs my sleep	87.9
I get exhausted easily	84.0

Section 4

Questions about other effects that your chest trouble may have on you these days.

Response	Weight
My cough or breathing is embarrassing in public	74.1
My chest trouble is a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot get my breath	87.7
I feel that I am not in control of my chest problem	90.1
I do not expect my chest to get any better	82.3
I have become frail or an invalid because of my chest	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

Response	Weight
My medication does not help me very much	88.2
I get embarrassed using my medication in public	53.9
I have unpleasant side effects from my medication	81.1
My medication interferes with my life a lot	70.3

Section 6

These are questions about how your activities might be affected by your breathing.

Response	Weight
I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time	81.0
I walk slower than other people, or I stop for rests	71.7
Jobs such as housework take a long time, or I have to stop for rests	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	63.5

Section 7

We would like to know how your chest usually affects your daily life.

Response	Weight
I cannot play sports or games	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81.0
I cannot do housework	79.1
I cannot move far from my bed or chair	94.0

Please write in any other important activities that your chest trouble may stop you doing (not used in total or domain score calculations):

Now would you tick in the box (one only) which you think best describes how your chest affects you:

Response	Weight
It does not stop me doing anything I would like to do	0.0
It stops me doing one or two things I would like to do	42.0
It stops me doing most of the things I would like to do	84.2
It stops me doing everything I would like to do	96.7

Scoring Algorithm

Three domain scores are calculated: **Symptoms, Activity, Impacts.**

One **Total** score is also calculated.

PRINCIPLE OF CALCULATION

Each questionnaire response (except where indicated) has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each domain of the questionnaire is scored separately in three steps:

i. The weights for all items with positive responses are summed.

ii The weights for missed items are deducted from the maximum possible weight for each domain. The weights for all missed items are deducted from the maximum possible weight for the Total score.

iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that domain and expressing the result as a percentage:

$$\text{Score} = \frac{\text{Summed weights from positive items in that domain}}{\text{Sum of weights for all items in that domain}} * 100$$

The Total score is calculated in similar way:

$$\text{Score} = \frac{\text{Summed weights from positive items in the questionnaire}}{\text{Sum of weights for all items in the questionnaire}} * 100$$

Sum of maximum possible weights for each domain and Total:

Symptoms	662.5
Activity	1209.1
Impacts	2117.8
Total	3989.4

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the subject).

SYMPTOMS DOMAIN

This is calculated from the summed weights for the positive responses to questions 1-8 of Part 1.

ACTIVITY DOMAIN

This is calculated from the summed weights for the positive responses to sections 2 and 6 of Part 2.

IMPACTS DOMAIN

This is calculated from the summed weights for the positive responses to sections 1, 3, 4, 5, 7 of Part 2.

TOTAL SCORE

The Total score is calculated by summing all positive responses in the questionnaire and expressing the result as a percentage of the total weight for the questionnaire.

HANDLING MISSING ITEMS

The following methods will be used:

Symptoms

The Symptoms domain will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms domain (662.5) and from the Total weight (3989.4).

Activity

The Activity domain will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity domain (1209.1) and from the Total weight (3989.4).

Impacts

The Impacts domain will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts domain (2117.8) and from the Total weight (3989.4).

Appendix 2: CCI [redacted]

[redacted] CCI [redacted]. Below scores for each item and other details for calculation are reported.

The values assigned to participants' responses for each question are listed below.

1) Performing vigorous activities, such as gardening or exercising

Response	Score
A lot of difficulty	1
Moderate difficulty	2
A little difficulty	3
No difficulty	4

2) Walking as fast as others (family, friends, etc.)

Response	Score
A lot of difficulty	1
Moderate difficulty	2
A little difficulty	3
No difficulty	4

3) Carrying heavy things, such as books or shopping bags.

Response	Score
A lot of difficulty	1
Moderate difficulty	2
A little difficulty	3
No difficulty	4

4) Climbing one flight of stairs.

Response	Score
A lot of difficulty	1
Moderate difficulty	2
A little difficulty	3
No difficulty	4

5) You felt well.

Response	Score	Reverse-coded Score
Always	1	4
Often	2	3
Sometimes	3	2
Never	4	1

6) You felt tired.

Response	**Score**
Always	1
Often	2
Sometimes	3
Never	4

7) You felt anxious.

Response	**Score**
Always	1
Often	2
Sometimes	3
Never	4

8) You felt energetic.

Response	**Score**	**Reverse-coded Score**
Always	1	4
Often	2	3
Sometimes	3	2
Never	4	1

9) You felt exhausted.

Response	**Score**
Always	1
Often	2
Sometimes	3
Never	4

10) You felt sad.

Response	**Score**
Always	1
Often	2
Sometimes	3
Never	4

11) You felt depressed.

Response	**Score**
Always	1
Often	2
Sometimes	3
Never	4

12) To what extent do your treatments for bronchiectasis make your daily life more difficult?

Response	Score	Reverse-coded Score
Not at all	1	4
A little	2	3
Moderately	3	2
A lot	4	1

13) How much time do you currently spend each day on your treatments for bronchiectasis?

Response	Score
A lot	1
A moderate amount	2
A little	3
Almost none	4

14) How difficult is it for you to fit in your treatments for bronchiectasis each day?

Response	Score	Reverse-coded Score
Not at all	1	4
A little	2	3
Moderately	3	2
Very	4	1

15) How do you think your health is now?

Response	Score	Reverse-coded Score
Excellent	1	4
Good	2	3
Fair	3	2
Poor	4	1

16) I have to limit vigorous activities, such as walking or exercising

Response	Score
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

17) I have to stay at home more than I want to

Response	Score

Completely true	1
Mostly true	2
A little true	3
Not at all true	4

18) I am worried about being exposed to other people who are ill

Response	**Score**
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

19) It is difficult to be intimate with a partner (kissing, hugging, etc)

Response	**Score**
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

20) I lead a normal life

Response	**Score**	**Reverse-coded Score**
Completely true	1	4
Mostly true	2	3
A little true	3	2
Not at all true	4	1

21) I am concerned that my health will get worse

Response	**Score**
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

22) I think my coughing bothers other people

Response	**Score**
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

23) I often feel lonely

Response	**Score**

Completely true	1
Mostly true	2
A little true	3
Not at all true	4

24) I feel healthy

Response	Score	Reverse-coded Score
Completely true	1	4
Mostly true	2	3
A little true	3	2
Not at all true	4	1

25) It is difficult to make plans for the future (holidays, attending family events, etc.)

Response	Score
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

26) I feel embarrassed when I am coughing

Response	Score
Completely true	1
Mostly true	2
A little true	3
Not at all true	4

27) To what extent did you have trouble keeping up with your job, housework, or other daily activities?

Response	Score	Reverse-coded Score
You have had no trouble keeping up	1	4
You have managed to keep up but it's been difficult	2	3
You have been behind	3	2
You have not been able to do these activities at all	4	1

28) How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?

Response	Score
Always	1
Often	2
Sometimes	3
Never	4

29) Have you felt congestion (fullness) in your chest?

Response	Score
A lot	1
A moderate amount	2
A little	3
Not at all	4

30) Have you been coughing during the day?

Response	Score
A lot	1
A moderate amount	2
A little	3
Not at all	4

31) Have you had to cough up sputum?

Response	Score
A lot	1
A moderate amount	2
A little	3
Not at all	4

32) Has your sputum been mostly:

Response	Score	Reverse-coded Score
Clear	1	4
Clear to yellow	2	3
Yellowish-green	3	2
Brownish-dark	4	1
Green with traces of blood	4	1
Don't know	6	Not Scored

33) Have you had shortness of breath when being more active, such as when doing housework or gardening?

Response	Score
Always	1
Often	2
Sometimes	3
Never	4

34) Have you been wheezing?

Response	Score
Always	1
Often	2
Sometimes	3
Never	4

35) Have you had chest pain?

Response	Score
Always	1
Often	2
Sometimes	3
Never	4

36) Have you had shortness of breath when talking?

Response	Score
Always	1
Often	2
Sometimes	3
Never	4

37) Have you woken up during the night because you were coughing?

Response	Score
Always	1
Often	2
Sometimes	3
Never	4

If two responses are marked the worst response should be selected for scoring. This provides a conservative estimate of the response to this item.
Missing values are not imputed. If the responses are missing for more than half the items in a scale, the score for that scale should not be calculated.

Item 32 (resp32) has 5 possible answers that are scored and all other items on the CCI [redacted] questionnaire have only 4 possible answers. Possible values for resp32 are 1, 2, 3, 4, 5 (scored as 4) and 6 (not scored), whereas for other questions the possible scores are 1, 2, 3, and 4. Resp32 and eight other items are also reverse coded; because of the wording for these particular items, reverse coding is necessary to make higher scores correspond to better health outcomes. Reverse coding is conducted for resp32, and for health5, vital8, treat12, treat14, health15, role20, health24 and role27. For those items the reverse score should be used in the analysis.

The following SAS code will be used to calculate scores for the eight CCI [redacted] domains. Note that a total CCI [redacted] score is not calculated.

- **Physical Functioning Domain**

5 items: 1, 2, 3, 4, 16

```
if nmiss (phys1, phys2, phys3, phys4, phys16) <= 2 then
physical = (mean (phys1, phys2, phys3, phys4, phys16)-1)/3*100;
```

- **Role Functioning Domain**

5 items: 17, 20, 25, 27, 28

```
if nmiss (role17, role20, role25, role27, role28) <= 2 then
role = (mean (role17, role20, role25, role27, role28)-1)/3*100;
```

- **Vitality Domain**

3 items: 6, 8, 9

```
if nmiss (vital6, vital8, vital9) <= 1 then
vitality = (mean (vital6, vital8, vital9)-1)/3*100;
```

- **Emotional Functioning Domain**

4 items: 7, 10, 11, 23

```
if nmiss (emot7, emot10, emot11, emot23) <= 2 then
emotion = (mean (emot7, emot10, emot11, emot23)-1)/3*100;
```

- **Social Functioning Domain**

4 items: 18, 19, 22, 26

```
if nmiss (social18, social19, social22, social26) <= 2 then
social = (mean (social18, social19, social22, social26)-1)/3*100;
```

- **Treatment Burden Domain**

3 items: 12, 13, 14

```
if nmiss (treat12, treat13, treat14) <= 1 then
treat = (mean (treat12, treat13, treat14)-1)/3*100;
```

- **Health Perceptions Domain**

4 items: 5, 15, 21, 24

```
if nmiss (health5, health15, health21, health24) <= 2 then
health = (mean (health5, health15, health21, health24)-1)/3*100;
```

- **Respiratory Symptoms Domain**

9 items: 29, 30, 31, 32, 33, 34, 35, 36, 37

```
if nmiss (resp29, resp30, resp31, resp32, resp33, resp34, resp35,
resp36, resp37) <= 4 then
respirat = (mean (resp29, resp30, resp31, resp32, resp33, resp34,
resp35, resp36, resp37)-1)/3*100;
```

Appendix 3: WHO-DD Preferred Terms for Antibiotics and Anti-Pseudomonal Antibiotics

COMMON ANTIBIOTICS WHO PT	ANTI-PSEUDOMONAL
ADENOMYCIN	
ADICILLIN	
ALATROFLOXACIN	
AMIKACIN	Y
AMIKACIN SULFATE	Y
AMOXICILLIN	
AMOXICILLIN SODIUM;CLAVULANATE POTASSIUM	
AMOXICILLIN TRIHYDRATE	
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	
AMOXICILLIN;CLAVULANATE POTASSIUM	
AMOXICILLIN;CLAVULANIC ACID	
AMPHOTERICIN B	
AMPICILLIN;SULBACTAM	
ASPOXICILLIN	
ASTROMICIN	
AVAROFLOXACIN	
AVIBACTAM	Y
AZIDOCILLIN	
AZITHROMYCIN	Y
AZITHROMYCIN DIHYDRATE	Y
AZTREONAM	Y
BACAMPICILLIN	
BALOFLOXACIN	
BEKANAMYCIN	
BENZYLPENICILLIN	
BENZYLPENICILLIN SODIUM	
BRODIMOPRIM	
CAFROLICYCLINE	
CARBENICILLIN	
CARBOMYCIN A	
CARINDACILLIN	
CARUMONAM	
CEFACETRILE	
CEFACLOR	Y

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COMMON ANTIBIOTICS WHO PT	ANTI-PSEUDOMONAL
CEFADROXIL	Y
CEFALEXIN	Y
CEFALOGLYCIN	
CEFALORIDINE	
CEFALOTIN	
CEFAMANDOLE	
CEFAPIRIN	
CEFATHIAMIDINE	
CEFATRIZINE	Y
CEFAZOLIN	Y
CEFAZOLIN SODIUM	Y
CEFEPIME	Y
CEFIXIME	Y
CEFRADINE	Y
CEFTAZIDIME	Y
CEFTAZIDIME/AVIBACTAM	Y
CEFTOLOZANE SULFATE;TAZOBACTAM SODIUM	Y
CEFTOLOZANE/TAZOBACTAM	Y
CEFTRIAXONE	Y
CEFTRIAXONE SODIUM	Y
CEFUROXIME	Y
CEFUROXIME AXETIL	Y
CHLORAMPHENICOL	
CIPROFLOXACIN	Y
CIPROFLOXACIN HYDROCHLORIDE	Y
CIPROFLOXACIN LACTATE	Y
CLARITHROMYCIN	Y
CLAVULANIC ACID	
CLINDAMYCIN	
CO-AMOXICLAV	
COLISTIMETHATE SODIUM	Y
COLISTIN	Y
COLISTIN SULFATE	Y
CO-TRIMOXAZOLE	
DORIPENEM	Y
DOXYCYCLINE	Y
DOXYCYCLINE HYDROCHLORIDE	Y
ERYTHROMYCIN	Y

COMMON ANTIBIOTICS WHO PT	ANTI-PSEUDOMONAL
FIDAXOMICIN	Y
FLUCLOXACILLIN	
FOSFOMYCIN	Y
FUSIDATE SODIUM	
GENTAMICIN	Y
IMIPENEM	Y
IMIPENEM/CILASTATIN	Y
LEVOFLOXACIN	Y
LINCOMYCIN HYDROCHLORIDE	
MEROPENEM	Y
MEROPENEM TRIHYDRATE	Y
METHENAMINE	
METHENAMINE HIPPURATE	
METRONIDAZOLE	
MOXIFLOXACIN	Y
MOXIFLOXACIN HYDROCHLORIDE	Y
NITROFURANTOIN	
OFLOXACIN	
PIPERACILLIN	Y
PIPERACILLIN SODIUM;TAZOBACTAM SODIUM	Y
PIPERACILLIN;TAZOBACTAM	Y
POLYMYXIN B	
ROXITHROMYCIN	Y
SULFAMETHOXAZOLE	
SULFAMETHOXAZOLE;TRIMETHOPRIM	
SULTAMICILLIN	
TAZOBACTAM	Y
TOBRAMYCIN	Y
TOBRAMYCIN SULFATE	Y
TRIMETHOPRIM	

Appendix 4: Macro Code for non-parametric ANCOVA

The non-parametric ANCOVA models will be fitted using the randomisation-based methodology as proposed by Koch et al [4] applying the macro written by Zink and Koch, reported below.

```
NParCov4
Non-Parametric Randomisation-Based Analysis of Covariance

PPD
JMP Life Sciences
SAS Institute, Inc.

and

PPD
Biometric Consulting Laboratory
Department of Biostatistics
University of North Carolina at Chapel Hill

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Inputs:

outcomes      List of outcome variables. Numeric.  At least 1 required. Need to be (0,1)
outcomes for
              LOGISTIC, PODDS, LOGRANK, WILCOXON

covars        List of covariates.  Numeric

exposures     Numeric exposure variables for (0,1) outcome for WILCOXON, LOGRANK and INCDENS.
              Need same number of variables as OUTCOMES.

strata        Variable that defines strata.  Numeric.  NONE (default) for no
              stratification (i.e. a single stratum)

trtgrps       Defines the treatments. Numeric. Differences defined
              are higher number (trt2) - lower number (trt1).  2 treatments required.

hypoth        NULL (default), ALT.  NULL groups treatments for estimating variance.
              ALT estimates variance within treatment

transform     NONE, LOGISTIC, PODDS, LOGRANK, LOGRATIO, WILCOXON, INCDENS.  Default is NONE.

combine       NONE, LAST, FIRST, PRETRANSFORM.  Only usable when strata is not NONE Default is
NONE.

c             Used in calculation of strata weights. 0 <= c <= 1. 0 assigns equal
              weights to strata, 1 is for Mantel-Haenszel weights. Default is 1.

alpha         For CI (0.05 default)

seed          Seed for exact p-values and confidence intervals.  (Default 0)

nreps         Number of random data sets to generate.  (Default 1000)

exact         NO (Default), YES. Must be NO for TRANSFORM = PODDS.  Only available
              for a single outcome. Under hypoth = ALT performs sampling with replacement
within treatment
              (bootstrap). Under hypoth = NULL performs sampling without replacement,
essentially shuffling
```

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```
              treatment codes among observations (permutation).

symsize       Define space requirements for IML (Default 20000)

dsnin         Input Data (required)

dsnout        Output data (required)

details       YES (default), NO.Print analysis details to the log.

************************************************************************************************
***************
************************************************************************************************
***************
************************************************************************************************
**************;

%macro NPARCOV4( outcomes = ,
                   covars = ,
                   strata = %str(NONE),
                  trtgrps = ,
                   hypoth = %str(NULL),
                transform = %str(NONE),
                  combine = %str(NONE),
                        c = 1,
                    dsnin = ,
                   dsnout = ,
                    alpha = 0.05,
                exposures =,
                     seed = 0,
                    nreps = 1000,
                  symsize = 20000,
                    exact = %str(NO),
                  details = %str(YES)
               );

   %global numstrat numtrts numobstot numresp numcov trt1 trt2 workoutcomes missind;

****************;
****************;
****************;

   %let outcomes = %upcase(&outcomes);
   %let strata = %upcase(&strata);
   %let exposures = %upcase(&exposures);
   %let covars = %upcase(&covars);

   %if ^%length(&dsnin) or ^%length(&dsnout) %then %do;
      %put ERROR: DSNIN and DSNOUT must be specified;
      %goto stopmac;
   %end;

   %if (%upcase(&hypoth) ne NULL) and (%upcase(&hypoth) ne ALT) %then %do;
      %put ERROR: HYPOTH must be specified as NULL or ALT;
      %goto stopmac;
   %end;

   %if (%upcase(&combine) ne NONE) and (%upcase(&strata) = NONE) %then %do;
      %put ERROR: STRATA = NONE so COMBINE should = NONE;
      %goto stopmac;
   %end;

   %if ^%index(NONE LOGISTIC PODDS LOGRATIO LOGRANK WILCOXON INCDENS, %upcase(&transform))
%then %do;
      %put ERROR: TRANSFORM must be one of NONE LOGISTIC PODDS LOGRATIO LOGRANK WILCOXON
INCDENS;
      %goto stopmac;
   %end;

   %if ^%index(NONE LAST FIRST PRETRANSFORM, %upcase(&combine)) %then %do;
      %put ERROR: COMBINE must be one of NONE LAST FIRST PRETRANSFORM;
```

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```
      %goto stopmac;
   %end;

   %if ^%length(&outcomes) %then %do;
      %put ERROR: OUTCOMES must have at least one variable specified;
      %goto stopmac;
   %end;

   %if ^%length(&trtgrps) %then %do;
      %put ERROR: TRTGRPS must be specified;
      %goto stopmac;
   %end;

   %if %sysevalf(&c < 0) or %sysevalf(&c > 1) %then %do;
      %put ERROR: C must be between 0 and 1, inclusive;
      %goto stopmac;
   %end;

   %if %sysevalf(&alpha < 0) or %sysevalf(&alpha > 1) %then %do;
      %put ERROR: ALPHA must be between 0 and 1;
      %goto stopmac;
   %end;

   %if ^%index(LOGRANK WILCOXON INCDENS, %upcase(&transform)) %then %do;
      %if %length(&exposures) ne 0 %then %do;
         %put ERROR: EXPOSURES should only be specified for WILCOXON LOGRANK INCDENS;
         %goto stopmac;
      %end;
   %end;

   %if %index(LOGRANK WILCOXON INCDENS, %upcase(&transform)) %then %do;
      %if ^%length(&exposures) %then %do;
         %put ERROR: EXPOSURES should be specified for WILCOXON LOGRANK INCDENS;
         %goto stopmac;
      %end;
   %end;

   %if ^%index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) and %upcase(&combine) =
PRETRANSFORM %then %do;
      %put ERROR: COMBINE = PRETRANSFORM only available for LOGRATIO LOGISTIC PODDS INCDENS;
      %goto stopmac;
   %end;

   %if %upcase(&strata) ne NONE and %upcase(&combine) = NONE %then %do;
      %put ERROR: STRATA specified but COMBINE = NONE;
      %goto stopmac;
   %end;

   %if ^%index(NO YES, %upcase(&exact)) %then %do;
      %put ERROR: EXACT must be one of NO YES;
      %goto stopmac;
   %end;

   %if %upcase(&transform) = PODDS and %upcase(&exact) = YES %then %do;
      %put ERROR: PODDS must have EXACT = NO;
      %goto stopmac;
   %end;

****************;
****************;
****************;

   ods noresults;

   data _null_;
      call symput("numresp", left(countw(compbl("&outcomes"), " ")));
      call symput("numcov", left(countw(compbl("&covars"), " ")));
      %if %index(LOGRANK WILCOXON INCDENS, %upcase(&transform)) %then %do;
         call symput("numtime", left(countw(compbl("&exposures"), " ")));
      %end;
      call symput("numstratwrd", left(countw(compbl("&strata"), " ")));
```

```
   run;

   %if %upcase(&exact) = YES and &numresp > 1 %then %do;
      %put ERROR: OUTCOMES can only have one variable for EXACT = YES;
      %goto stopmac;
   %end;

   %if %sysevalf(&numstratwrd ne 1) %then %do;
      %put ERROR: STRATA can only have a single variable specified;
      %goto stopmac;
   %end;

   %if %index(LOGRANK WILCOXON INCDENS, %upcase(&transform)) %then %do;
      %if &numtime ne &numresp %then %do;
         %put ERROR: EXPOSURES and RESPONSE must have same number of variables specified for
WILCOXON LOGRANK INCDENS;
         %goto stopmac;
      %end;
   %end;

   %if %index(LOGRANK WILCOXON, %upcase(&transform)) %then %do;
      %let workoutcomes = ;
      %do i = 1 %to &numresp;
         %let tempoutcomes = &transform._%scan(&outcomes, &i);
         %let workoutcomes = &workoutcomes &tempoutcomes;
      %end;
   %end;
   %else %if %index(INCDENS, %upcase(&transform)) %then %do;
      %let workoutcomes = ;
      %do i = 1 %to &numresp;
         %let tempoutcomes = INC_%scan(&outcomes, &i);
         %let workoutcomes = &workoutcomes &tempoutcomes;
      %end;
   %end;
   %else %do;
      %let workoutcomes = &outcomes;
   %end;

   data _work_temp;
      set &dsnin end = eof;
      %if %upcase(&strata) = NONE or %upcase(&combine) = NONE %then %do;
         _NONE = 1;
      %end;
      if eof then call symput("numobstot", left(_n_));
   run;

   %if %index(LOGRANK WILCOXON PODDS LOGISTIC, %upcase(&transform)) %then %do;
      %do i = 1 %to &numresp;
         proc freq noprint data = _work_temp;
            tables %scan(&outcomes,&i) / out = binarychk;
         run;

         proc means n sum noprint data = binarychk;
            var %scan(&outcomes,&i);
            output out = binarychk n = nbinchk sum = sumbinchk;
         run;

         data _null_;
            set binarychk;
            call symput("nbinchk", left(nbinchk));
            call symput("sumbinchk", left(sumbinchk));
         run;

         %if not(&nbinchk = 2 and &sumbinchk = 1) %then %do;
            %put ERROR: %upcase(%scan(&outcomes,&i)) not a (0,1) OUTCOME;
            %goto stopmac;
         %end;
      %end;

      proc datasets nolist;
         delete binarychk;
```

```
      quit;
   %end;

   %if %upcase(&strata) = NONE %then %do;
      %MISSDAT(varlist = &outcomes &covars &trtgrps &exposures, data = _work_temp);
   %end;
   %else %do;
      %MISSDAT(varlist = &outcomes &covars &strata &trtgrps &exposures, data = _work_temp);
   %end;
   %if &missind %then %do;
      %put ERROR: Missing values are present in at least one of OUTCOMES COVARS STRATA TRTGRPS
EXPOSURES;
      %goto stopmac;
   %end;

   %if %index(INCDENS, %upcase(&transform)) %then %do;
      data _work_temp;
         set _work_temp(rename = (%do i = 1 %to &numresp; %scan(&outcomes, &i) =
%scan(&workoutcomes, &i) %end;));
      run;
   %end;

   proc freq nlevels data = _work_temp;
      ods exclude all;
      ods output NLevels = _work_ntrts_chk;
      tables &trtgrps;
   run;
   ods select all;

   data _null_;
      set _work_ntrts_chk;
      call symput("numtrtlevels", left(nlevels));
   run;

   %if &numtrtlevels ne 2 %then %do;
      %put ERROR: TRTGRPS must have TWO levels;
      %goto stopmac;
   %end;

   %if %upcase(&strata) = NONE or %upcase(&combine) = NONE %then %do;
      %let strata = _NONE;
   %end;

   proc freq noprint data = _work_temp;
      tables &trtgrps / out = _work_ntrts;
   run;

   data _null_;
      set _work_ntrts;
      if _n_ = 1 then call symput("trt1", trim(left(&trtgrps)));
      else if _n_ = 2 then call symput("trt2", trim(left(&trtgrps)));
   run;

   %if %upcase(&transform) = LOGRANK or %upcase(&transform) = WILCOXON %then %do;
      %SURVSCORE(eventlist = &outcomes, timelist = &exposures, score = %upcase(&transform));
   %end;

   proc sort data = _work_temp;
      by &strata &trtgrps;
   run;

   proc sql noprint;
      select distinct &strata
      into :stratalist separated by ','
      from _work_temp;
   quit;

   proc freq nlevels data = _work_temp;
      ods exclude all;
      ods output NLevels = _work_nstrt;
      tables &strata;
```

```
   run;
   ods select all;

   data _null_;
      set _work_nstrt;
      call symput("numstrat", left(nlevels));
   run;

   proc freq noprint data = _work_temp;
       tables &trtgrps * &strata / out = _work_trtstrat_chk(drop = percent);
   run;

   proc means min n noprint data = _work_trtstrat_chk;
      var count;
      where count > 0;
      output out = _work_trtstrat_chk n = trtstratcount min = trtstratmin;
   run;

   data _null_;
      set _work_trtstrat_chk;
      call symput("treatin", left(trtstratcount));
      call symput("treatinmin", left(trtstratmin));
   run;

   %if &treatin ^= %sysevalf(2 * &numstrat) %then %do;
      %put ERROR: Both TRTGRPS should be present in all strata;
      %goto stopmac;
   %end;

   %if &treatinmin = 1 and %upcase(&hypoth) = ALT %then %do;
      %put ERROR: Need at least two observations for each strata*treatment combination for
variance estimation under HYPOTH = ALT;
      %goto stopmac;
   %end;

   proc datasets nolist;
      delete _work_trtstrat_chk;
   quit;

   %if %upcase(&details) = YES %then %do;
      %put NOTE NOTE NOTE:  Treatment1 = &trt1 and Treatment2 = &trt2;
      %put NOTE NOTE NOTE:  Total Number of OBSERVATIONS for BOTH TREATMENTS: &numobstot;
      %put NOTE NOTE NOTE:  Number of RESPONSE VARIABLES: &numresp;
      %put NOTE NOTE NOTE:  Number of COVARIATES: &numcov;
      %put NOTE NOTE NOTE:  Number of STRATA: &numstrat;
   %end;

   %if %upcase(&exact) = YES and %upcase(&hypoth) = ALT %then %do;
      proc sort data = _work_temp;
         by &trtgrps;
      run;
   %end;

   %if %upcase(&exact) = YES %then %do;
      proc multtest %if %upcase(&hypoth) = NULL %then %do; permutation %end; %else %do;
bootstrap %end;
         nocenter noprint seed = &seed nsample = &nreps outsamp = _work_outsamp(drop = _obs_)
data = _work_temp;
         class &trtgrps;
         strata &strata;
         %if %upcase(&hypoth) = ALT %then %do;
            ***** select samples within treatment under alternative *****;
            by &trtgrps;
         %end;
          %if %upcase(&transform) = INCDENS %then %do;
            test mean (&workoutcomes &exposures &covars);
          %end;
          %else %do;
            test mean (&workoutcomes &covars);
          %end;
      run;
```

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```
   data _work_outsamp(drop = _class_ _stratum_);
      set _work_outsamp %if %upcase(&hypoth) = ALT %then %do; (drop = &trtgrps) %end;;
      &trtgrps = _class_ + 0;
      &strata = _stratum_ + 0;
   run;

   proc sort data = _work_outsamp;
      by _sample_ &strata &trtgrps;
   run;
%end;

%if %upcase(&exact) = YES and %upcase(&hypoth) = ALT %then %do;
   proc sort data = _work_temp;
      by &strata &trtgrps;
   run;

   data _work_jack(drop = i);
      do i = 1 to &numobstot;
         _sample_ = i + &nreps;
         do j = 1 to &numobstot;
            if j ne i then do;
               set _work_temp point = j;
               output;
               end;
            end;
         end;
      stop;
   run;
%end;

data _work_temp;
   set _work_temp(in = ina)
   %if %upcase(&exact) = YES %then %do;
      _work_outsamp(in = inb)
      %if (%upcase(&exact) = YES and %upcase(&hypoth) = ALT) %then %do;
         _work_jack(in = inc)
      %end;
   %end;
   ;
   if ina then _sample_ = 0;
run;

***** Means *****;

proc sort data = _work_temp;
   by _sample_ &strata &trtgrps;
run;

proc means mean noprint data = _work_temp;
   %if %upcase(&transform) = INCDENS %then %do;
      var &workoutcomes &exposures &covars;
   %end;
   %else %do;
      var &workoutcomes &covars;
   %end;
   by _sample_ &strata &trtgrps;
   %if %upcase(&transform) = INCDENS %then %do;
      output out = _work_means mean = &workoutcomes &exposures &covars;
   %end;
   %else %do;
      output out = _work_means mean = &workoutcomes &covars;
   %end;
run;

***** Covariances *****;

proc corr cov outp = _work_covar(where = (_type_ = 'COV')) noprint data = _work_temp;
   %if %upcase(&transform) = INCDENS %then %do;
      var &workoutcomes &exposures &covars;
   %end;
```

```
      %else %do;
         var &workoutcomes &covars;
      %end;
      %if %upcase(&hypoth) = ALT %then %do;
         by _sample_ &strata &trtgrps;
      %end;
      %else %if %upcase(&hypoth) = NULL %then %do;
         by _sample_ &strata;
      %end;
   run;

   %if %upcase(&hypoth) = NULL %then %do;
      data _work_covar;
         set _work_covar(in = ina) _work_covar(in = inb);
         if ina then &trtgrps = "&trtl";
         else if inb then &trtgrps = "&trt2";
      run;

      proc sort data = _work_covar;
         by _sample_ &strata &trtgrps;
      run;
   %end;

****************;
****************;
****************;

*** Output Data ***;

%if &numcov >= 1 %then %do;
   data _&dsnout._covtest;
      length type $ 10 trtl trt2 strata covariates outcomes exposures $ 50 hypothesis $ 4;
      format h df 8.0 Q 8.4 pvalue pvalue8.4;
      %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) = 0 %then %do;
         drop exposures;
      %end;
   run;
%end;

data _&dsnout._deptest;
   length type $ 10 transform trtl trt2 strata covariates outcomes exposures $ 50 hypothesis $
4;
   format h df 8.0 beta sebeta Q_j ratio 8.4 pvalue pvalue8.4;
   %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) = 0 %then %do;
      drop exposures;
   %end;
   %if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) = 0 %then %do;
      drop ratio;
   %end;
run;

%if %upcase(&hypoth) = ALT %then %do;
   data _&dsnout._ci;
      length type $ 10 trtl trt2 strata covariates outcomes exposures $ 50 hypothesis $ 4;
      format h 8.0 beta sebeta lower upper 8.4 alpha 8.2;
      %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) = 0 %then %do;
         drop exposures;
      %end;
   run;
%end;

%if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) > 0 and %upcase(&hypoth) =
ALT %then %do;
   data _&dsnout._ratioci;
      length type $ 10 trtl trt2 strata covariates outcomes exposures $ 50 hypothesis $ 4;
      format h 8.0 ratio ratio_lower ratio_upper 8.4 alpha 8.2;
      %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) = 0 %then %do;
         drop exposures;
      %end;
      run;
%end;
```

```
%if %index(PODDS, %upcase(&transform)) > 0 %then %do;
   data _&dsnout._homogen;
      length type $ 10 trt1 trt2 strata covariates outcomes $ 50;
      format df 8.0 Q_c 8.4 pvalue pvalue8.4;
   run;
%end;

%if %upcase(&exact) = YES %then %do;
   data _&dsnout._exact;
      length type $ 10 trt1 trt2 strata covariates outcomes $ 50 hypothesis $ 4;
      format twosided one_lower one_upper pvalue8.4 h nreps seed 8.0 bias accel bca_lower
bca_upper pct_lower pct_upper alpha_low alpha_hi 8.6 seed 8.0;
      %if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) and &hypoth = ALT %then
%do;
         format bca_ratio_lower bca_ratio_upper pct_ratio_lower pct_ratio_upper 8.6;
      %end;
      %if &hypoth = NULL %then %do;
          drop bias accel bca_upper bca_lower alpha_hi alpha_low pct_lower pct_upper;
      %end;
   run;
%end;

****************;
****************;
****************;

   proc iml symsize = &symsize;
      start NPARCOV4(h, r, t, c, hypoth, f, V, n, varnames, combine, transform);
         wh = CREATEWH(h, c, n);
         if t>0 then X = I(r)//J(t,r,0);
         else if t=0 then X = I(r);

         if transform = 'LOGISTIC' & combine = 'PRETRANSFORM' then run TRANSFIRST(h, r, t, n,
f, wh, V, X, hypoth, varnames, 0, 0, 'LOGISTIC');
         else if transform = 'PODDS' & combine = 'PRETRANSFORM' then run PROTRANSFIRST(h, r,
t, n, f, wh, V, X, hypoth, varnames);
         else if transform = 'LOGRATIO' & combine = 'PRETRANSFORM' then run TRANSFIRST(h, r,
t, n, f, wh, V, X, hypoth, varnames, 0, 0, 'LOGRATIO');
         else if transform = 'INCDENS' & combine = 'PRETRANSFORM' then run TRANSFIRST(h, r, t,
n, f, wh, V, X, hypoth, varnames, 0, 0, 'INCDENS');
         else do;
            if (transform = 'LOGISTIC' | transform = 'PODDS') & combine ^= 'PRETRANSFORM' then
run TRANSFORM(h, r, t, f, V, hypoth, n, 'LOGISTIC');
            else if (transform = 'LOGRATIO') & combine ^= 'PRETRANSFORM' then run TRANSFORM(h,
r, t, f, V, hypoth, n, 'LOGRATIO');
            else if (transform = 'INCDENS') & combine ^= 'PRETRANSFORM' then run TRANSFORM(h,
r, t, f, V, hypoth, n, 'INCDENS');

            Vdh = VARSTRAT(h, r, t, V, n);
            dh = CREATEDH(h, r, t, f);

            if transform = 'LOGRANK' & (combine = 'LAST' | combine = 'NONE') then run LAST(n,
h, r, t, dh, wh, Vdh, X, hypoth, varnames, 0, 0, 0);
            else if transform = 'LOGRANK' & combine = 'FIRST' then run FIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames, 0, 0, 0);
            else if transform = 'WILCOXON' & (combine = 'LAST' | combine = 'NONE') then run
LAST(n, h, r, t, dh, wh, Vdh, X, hypoth, varnames, 0, 0, 0);
            else if transform = 'WILCOXON' & combine = 'FIRST' then run FIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames, 0, 0, 0);
            else if transform = 'LOGISTIC' & (combine = 'LAST' | combine = 'NONE') then run
LAST(n, h, r, t, dh, wh, Vdh, X, hypoth, varnames, 0, 0, 1);
            else if transform = 'LOGISTIC' & combine = 'FIRST' then run FIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames, 0, 0, 1);
            else if transform = 'LOGRATIO' & (combine = 'LAST' | combine = 'NONE') then run
LAST(n, h, r, t, dh, wh, Vdh, X, hypoth, varnames, 0, 0, 1);
            else if transform = 'LOGRATIO' & combine = 'FIRST' then run FIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames, 0, 0, 1);
            else if transform = 'PODDS' & combine = 'FIRST' then run PROFIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames);
```

```
            else if transform = 'PODDS' & (combine = 'LAST' | combine = 'NONE') then run
PROLAST(h, r, t, dh, wh, Vdh, X, hypoth, varnames);
            else if transform = 'NONE' & (combine = 'LAST' | combine = 'NONE') then run
LAST(n, h, r, t, dh, wh, Vdh, X, hypoth, varnames, 0, 0, 0);
            else if transform = 'NONE' & combine = 'FIRST' then run FIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames, 0, 0, 0);
            else if transform = 'INCDENS' & (combine = 'LAST' | combine = 'NONE') then run
LAST(n, h, r, t, dh, wh, Vdh, X, hypoth, varnames, 0, 0, 1);
            else if transform = 'INCDENS' & combine = 'FIRST' then run FIRST(h, r, t, dh, wh,
Vdh, X, hypoth, varnames, 0, 0, 1);
         end;
      finish NPARCOV4;

****************;
****************;
****************;

      start VARSTRAT(h, r, t, V, n);
         VAR = J(h*(r+t), r+t, 0);
         count = 1;
         do i = 1 to h;
            VAR[1+(i-1)*(r+t):i*(r+t),] = V[1+(count-1)*(r+t):count*(r+t),] / n[count] +
V[1+(count)*(r+t):(count+1)*(r+t),] / n[count+1];
            count = count + 2;
         end;
         return(VAR);
      finish VARSTRAT;

****************;
****************;
****************;

      start CREATEDH(h, r, t, f);
         D = J(h*(r+t), 1, 0);
         count = 1;
         do i = 1 to h;
            D[1+(i-1)*(r+t):i*(r+t)] =  - f[1+(count-1)*(r+t):count*(r+t)] +
f[1+(count)*(r+t):(count+1)*(r+t)];
            count = count + 2;
         end;
         return(D);
      finish CREATEDH;

****************;
****************;
****************;

      start CREATEWH(h, c, n);
         wh = J(h, 1, 0);
         count = 1;
         do i = 1 to h;
            wh[i] = ( (n[count] * n[count+1])/(n[count] + n[count+1]) ) ## c;
            count = count + 2;
         end;
         return(wh);
      finish CREATEWH;

****************;
****************;
****************;

      start LAST(nval, h, r, t, dh, wh, Vdh, X, hypoth, varnames, homoyes, proptitl,
oddsrats);
         betaall = J(h*NCOL(X), 1, 0);
         vbetaall = J(h*NCOL(X), NCOL(X), 0);
         if t > 0 then Q = 0;

         n_h = J(h, 1, 0);
         count = 1;
         do i = 1 to h;
            VEE = Vdh[1+(i-1)*(r+t):i*(r+t),];
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            dee = dh[1+(i-1)*(r+t):i*(r+t)];
            betaall[1+(i-1)*NCOL(X):i*NCOL(X)] = ESTIMATE(X, VEE, dee);
            vbetaall[1+(i-1)*NCOL(X):i*NCOL(X),] = VAREST(X, VEE);

            n_h[i] = nval[count] + nval[count+1];
            count = count + 2;

            if t > 0 then do;
               run COVTESTS(dee, VEE, X, betaall[1+(i-1)*NCOL(X):i*NCOL(X)], t, varnames,
Qpart, 0, proptitl, h);
               Q = Q + Qpart;
            end;
         end;

         if h > 1 then do;
            strata_h = {&stratalist};
            beta_h = betaall;
            create _&dsnout._stratabeta var{strata_h,beta_h,n_h};
               append;
            close _&dsnout._stratabeta;
            free beta_h strata_h;
         end;

         beta = WGTSUM(h, betaall, wh, 1);
         varbeta = WGTSUM(h, vbetaall, wh, 2);

         create _&dsnout._covbeta from varbeta[colname = varnames];
            append from varbeta;
         close _&dsnout._covbeta;

         if t > 0 & homoyes = 0 then do;
            df = (NROW(X) - NCOL(X))*h;
            pvalue = 1 - PROBCHI(Q, df);
            edit _&dsnout._covtest;
            type = "COVTEST";
            trt1 = "&trt1";
            trt2 = "&trt2";
            %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) %then %do;
               exposures = "&exposures";
            %end;
            outcomes = "&workoutcomes";
            covariates = "&covars";
            strata = "&strata";
            hypothesis = "&hypoth";
            append;
            close _&dsnout._covtest;
         end;

         if homoyes = 0 then run DEPTESTS(beta, varbeta, varnames, ncol(X));
         if hypoth = 'ALT' & homoyes = 0 then run CI(beta, varbeta, varnames, oddsrats,
ncol(X));
         if homoyes = 1 then run HOMOGEN(beta, varbeta);
      finish LAST;

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      start ESTIMATE(X, V, d);
         return(INV(X`*INV(V)*X)*X`*INV(V)*d);
      finish ESTIMATE;

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****************;

      start VAREST(X, V);
         return(INV(X`*INV(V)*X));
      finish VAREST;

****************;
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```
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*****************;

      start COVTESTS(d, Vd, X, beta, t, varnames, Q, printyes, proptitl, h);
         Q = (d - X*beta)` * INV(Vd) * (d - X*beta);
         df = NROW(X)-NCOL(X);
         pvalue = 1 - PROBCHI(Q, df);

         if printyes = 1 then do;
            edit _&dsnout._covtest;
            type = "COVTEST";
            trt1 = "&trt1";
            trt2 = "&trt2";
            covariates = "&covars";
            %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) %then %do;
               exposures = "&exposures";
            %end;
            outcomes = "&workoutcomes";
            strata = "&strata";
            hypothesis = "&hypoth";
            append;
            close _&dsnout._covtest;
         end;
      finish COVTESTS;

*****************;
*****************;
*****************;

      start DEPTESTS(beta, varbeta, varnames, num);
         sebeta = sqrt(VECDIAG(varbeta));
         Q_j = beta##2/VECDIAG(varbeta);
         df = J(NROW(beta), 1, 1);
         pvalue = 1 - PROBCHI(Q_j, df);
         outcomes = varnames[1:num]`;
         %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) %then %do;
            exposures = {&exposures}`;
         %end;
         %if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) %then %do;
            ratio = exp(beta);
         %end;
         edit _&dsnout._deptest;
         transform = J(NROW(beta), 1, "&transform");
         type = J(NROW(beta), 1, "DEPTEST");
         trt1 = J(NROW(beta), 1, "&trt1");
         trt2 = J(NROW(beta), 1, "&trt2");
         covariates = J(NROW(beta), 1, "&covars");
         h = J(NROW(beta), 1, &numstrat);
         strata = J(NROW(beta), 1, "&strata");
         label = J(NROW(beta), 1, "Test Between Groups for Outcomes");
         hypothesis = J(NROW(beta), 1, "&hypoth");
         append;
         close _&dsnout._deptest;
      finish DEPTESTS;

*****************;
*****************;
*****************;

      start CI(beta, varbeta, varnames, oddsrats, num);
         sebeta = sqrt(VECDIAG(varbeta));
         lower = beta - probit(%sysevalf(1-&alpha/2))*sebeta;
         upper = beta + probit(%sysevalf(1-&alpha/2))*sebeta;

         edit _&dsnout._ci;
         outcomes = varnames[1:num]`;
         %if %index(INCDENS LOGRANK WILCOXON, %upcase(&transform)) %then %do;
            exposures = {&exposures}`;
         %end;
         type = J(NROW(beta), 1, "CI");
         trt1 = J(NROW(beta), 1, "&trt1");
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```
         trt2 = J(NROW(beta), 1, "&trt2");
         covariates = J(NROW(beta), 1, "&covars");
         h = J(NROW(beta), 1, &numstrat);
         alpha = J(NROW(beta), 1, &alpha);
         strata = J(NROW(beta), 1, "&strata");
         hypothesis = J(NROW(beta), 1, "&hypoth");
         append;
         close _&dsnout._ci;

         if oddsrats=1 then do;
            ratio = EXP(beta);
            ratio_lower = EXP(lower);
            ratio_upper = EXP(upper);

            edit _&dsnout._ratioci;
            type = J(NROW(beta), 1, "RATIOCI");
            trt1 = J(NROW(beta), 1, "&trt1");
            trt2 = J(NROW(beta), 1, "&trt2");
            covariates = J(NROW(beta), 1, "&covars");
            h = J(NROW(beta), 1, &numstrat);
            alpha = J(NROW(beta), 1, &alpha);
            strata = J(NROW(beta), 1, "&strata");
            hypothesis = J(NROW(beta), 1, "&hypoth");
            append;
            close _&dsnout._ratioci;
         end;
      finish CI;

****************;
****************;
****************;

      start WGTSUM(h, mats, wh, expo);
         total = J(NROW(mats)/h, NCOL(mats), 0);
         do i = 1 to h;
            total = total + (wh[i] ## expo) * mats[1+(i-1)*(NROW(mats)/h):i*(NROW(mats)/h),];
         end;
         total = total / (sum(wh) ## expo);
         return(total);
      finish WGTSUM;

****************;
****************;
****************;

      start WGTSUM2(h, r, t, mats, wh, expo);
         total = J(2*(r+t), NCOL(mats), 0);
         count = 1;
         do i = 1 to h;
            total[1:(r+t),] = total[1:(r+t),] + (wh[i] ## expo) * mats[1+(count-
1)*(r+t):count*(r+t),];
            total[(r+t+1):2*(r+t),] = total[(r+t+1):2*(r+t),] + (wh[i] ## expo) *
mats[1+count*(r+t):(count+1)*(r+t),];
            count = count + 2;
         end;
         total = total / (sum(wh) ## expo);
         return(total);
      finish WGTSUM2;

****************;
****************;
****************;

      start FIRST(h, r, t, dh, wh, Vdh, X, hypoth, varnames, homoyes, proptitl, oddsrats);
         d = WGTSUM(h, dh, wh, 1);
         Vd = WGTSUM(h, Vdh, wh, 2);
         beta = ESTIMATE(X, Vd, d);
         varbeta = VAREST(X, Vd);
         create _&dsnout._covbeta from varbeta[colname = varnames];
            append from varbeta;
         close _&dsnout._covbeta;
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         if t > 0 & homoyes = 0 then run COVTESTS(d, Vd, X, beta, t, varnames, Q, 1, proptitl,
h);
         if homoyes = 0 then run DEPTESTS(beta, varbeta, varnames, ncol(X));
         if hypoth = 'ALT' & homoyes = 0 then run CI(beta, varbeta, varnames, oddsrats,
ncol(X));
         if homoyes = 1 then run HOMOGEN(beta, varbeta);
      finish FIRST;

****************;
****************;
****************;

      start PROFIRST(h, r, t, dh, wh, Vdh, X, hypoth, varnames);
         run FIRST(h, r, t, dh, wh, Vdh, X, hypoth, varnames, 1, 1, 1);
         X = J(r+t, 1, 0);
         X[1:r] = 1;
         newname = J(t+1, 1, 'TREATMENT');
         if t > 0 then newname[2:t+1] = varnames[r+1:r+t];
         run FIRST(h, r, t, dh, wh, Vdh, X, hypoth, newname, 0, 1, 1);
      finish PROFIRST;

****************;
****************;
****************;

      start PROLAST(h, r, t, dh, wh, Vdh, X, hypoth, varnames);
         run LAST(h, r, t, dh, wh, Vdh, X, hypoth, varnames, 1, 0, 1);
         X = J(r+t, 1, 0);
         X[1:r] = 1;
         newname = J(t+1, 1, 'TREATMENT');
         if t > 0 then newname[2:t+1] = varnames[r+1:r+t];
         run LAST(h, r, t, dh, wh, Vdh, X, hypoth, newname, 0, 1, 1);
      finish PROLAST;

****************;
****************;
****************;

      start TRANSFIRST(h, r, t, n, f, wh, V, X, hypoth, varnames, homoyes, proptitl,
transtype);
         %if %index(LOGISTIC LOGRATIO, %upcase(&transform)) > 0 %then %do;
            VEE = J(2*h*(r+t), r+t, 0);

            do i = 1 to 2*h;
               VEE[1+(i-1)*(r+t):i*(r+t),] = V[1+(i-1)*(r+t):i*(r+t),] / n[i];
            end;

            fstar = WGTSUM2(h, r, t, f, wh, 1);
            Vstar = WGTSUM2(h, r, t, VEE, wh, 2);
         %end;
         %else %if %index(INCDENS, %upcase(&transform)) %then %do;
            VEE = J(2*h*(2*r+t), 2*r+t, 0);

            do i = 1 to 2*h;
               VEE[1+(i-1)*(2*r+t):i*(2*r+t),] = V[1+(i-1)*(2*r+t):i*(2*r+t),] / n[i];
            end;

            fstar = WGTSUM2(h, 2*r, t, f, wh, 1);
            Vstar = WGTSUM2(h, 2*r, t, VEE, wh, 2);
         %end;
         run TRANSFORM(1, r, t, fstar, Vstar, hypoth, n, transtype);
         Vdh = VARSTRAT(1, r, t, Vstar, J(2,1,1));
         dh = CREATEDH(1, r, t, fstar);

         run FIRST(1, r, t, dh, 1, Vdh, X, hypoth, varnames, homoyes, proptitl, 1);
      finish TRANSFIRST;

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****************;
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```
      start PROTRANSFIRST(h, r, t, n, f, wh, V, X, hypoth, varnames);
         run TRANSFIRST(h, r, t, n, f, wh, V, X, hypoth, varnames, 1, 0, 'LOGISTIC');
         X = J(r+t, 1, 0);
         X[1:r] = 1;
         newname = J(t+1, 1, 'TREATMENT');
         if t > 0 then newname[2:t+1] = varnames[r+1:r+t];
         run TRANSFIRST(h, r, t, n, f, wh, V, X, hypoth, newname, 0, 1, 'LOGISTIC');
      finish PROTRANSFIRST;

****************;
****************;
****************;

      start HOMOGEN(beta, varbeta);
         C = I(NROW(beta)-1)||J(NROW(beta)-1, 1, -1);
         Q_c = beta` * C` * INV(C * varbeta * C`) * C * beta;
         df = NROW(beta) - 1;
         pvalue = 1 - PROBCHI(Q_c, df);
         outcomes = "TREATMENT";

         edit _&dsnout._homogen;
            type = "HOMOGEN";
            trt1 = "&trt1";
            trt2 = "&trt2";
            covariates = "&covars";
            strata = "&strata";
            hypoth = "&hypoth";
            append;
         close _&dsnout._homogen;
      finish HOMOGEN;

****************;
****************;
****************;

      start TRANSFORM(h, r, t, f, V, hypoth, n, transtype);
         if hypoth = 'ALT' then run TRANSVARALT(h, r, t, f, V, transtype);
         else if hypoth = 'NULL' then run TRANSVARNULL(h, r, t, f, V, n, transtype);
         run TRANSF(h, r, t, f, transtype);
      finish TRANSFORM;

****************;
****************;
****************;

      start TRANSVARALT(h, r, t, f, V, transtype);
         if transtype = "LOGISTIC" | transtype = "LOGRATIO" then do;
            d = J(r+t, 1, 0);
            if t > 0 then d[r+1:r+t] = 1;
            do i = 1 to 2*h;
               temp = f[1+(i-1)*(r+t):(i*r)+(i-1)*t];
               if transtype = "LOGISTIC" then d[1:r] = 1/(f[1+(i-1)*(r+t):(i*r)+(i-1)*t]#(1-
f[1+(i-1)*(r+t):(i*r)+(i-1)*t]));
               else if transtype = "LOGRATIO" then d[1:r] = 1/f[1+(i-1)*(r+t):(i*r)+(i-1)*t];
               V[1+(i-1)*(r+t):i*(r+t),] = (V[1+(i-1)*(r+t):i*(r+t),] # d) # d`;
            end;
         end;
         else if transtype = "INCDENS" then do;
            Vtemp = J(2*h*(r+t), (r+t), 0);
            do i = 1 to 2*h;
               dy = diag(1/f[1+(i-1)*(2*r+t):(i*r)+(i-1)*(r+t)]);
               dt = -diag(1/f[(r+1)+(i-1)*(2*r+t):(2*i*r)+(i-1)*t]);
               if t = 0 then M = dy||dt;
               else do;
                  top = dy||dt||J(r,t,0);
                  bottom = J(t,2*r,0)||I(t);
                  M = top // bottom;
                  free top bottom;
               end;
               Vtemp[1+(i-1)*(r+t):i*(r+t),] = M * V[1+(i-1)*(2*r+t):i*(2*r+t),] * M`;
            end;
```

```
            V = Vtemp;
            free Vtemp M;
         end;
      finish TRANSVARALT;

****************;
****************;
****************;

      start TRANSVARNULL(h, r, t, f, V, n, transtype);
         if transtype = "LOGISTIC" | transtype = "LOGRATIO" then do;
            d = J(r+t, 1, 0);
            if t > 0 then d[r+1:r+t] = 1;
            count = 1;
            do i = 1 to h;
               ybar = (n[count] * f[1+(count-1)*(r+t):(count*r)+(count-1)*t] + n[count+1] *
f[1+(count)*(r+t):((count+1)*r)+(count)*t]) /
                      (n[count] + n[count+1]);
               if transtype = "LOGISTIC" then d[1:r] = 1/(ybar # (1-ybar));
               else if transtype = "LOGRATIO" then d[1:r] = 1/ybar;
               V[1+(count-1)*(r+t):count*(r+t),] = (V[1+(count-1)*(r+t):count*(r+t),] # d) #
d`;
               V[1+(count)*(r+t):(count+1)*(r+t),] = (V[1+(count)*(r+t):(count+1)*(r+t),] # d)
# d`;
               count = count + 2;
            end;
         end;
         else if transtype = "INCDENS" then do;
            Vtemp = J(2*h*(r+t), (r+t), 0);
            count = 1;
            do i = 1 to h;
               ytbar = (n[count] * f[1+(count-1)*(2*r+t):(count*2*r)+(count-1)*t] + n[count+1]
* f[1+(count)*(2*r+t):((count+1)*2*r)+(count)*t]) /
                        (n[count] + n[count+1]);
               dy = diag(1/ytbar[1:r]);
               dt = -diag(1/ytbar[r+1:2*r]);
               if t = 0 then M = dy||dt;
               else do;
                  top = dy||dt||J(r,t,0);
                  bottom = J(t,2*r,0)||I(t);
                  M = top // bottom;
                  free top bottom;
               end;
               Vtemp[1+(count-1)*(r+t):count*(r+t),] = M * V[1+(count-
1)*(2*r+t):count*(2*r+t),] * M`;
               Vtemp[1+(count)*(r+t):(count+1)*(r+t),] = M *
V[1+(count)*(2*r+t):(count+1)*(2*r+t),] * M`;
               count = count + 2;
            end;
            V = Vtemp;
            free Vtemp M;
         end;
      finish TRANSVARNULL;

****************;
****************;
****************;

      start TRANSF(h, r, t, f, transtype);
         do i = 1 to 2*h;
            if transtype = "LOGISTIC" then f[1+(i-1)*(r+t):(i*r)+(i-1)*t] = LOG(f[1+(i-
1)*(r+t):(i*r)+(i-1)*t] / (1 - f[1+(i-1)*(r+t):(i*r)+(i-1)*t]));
            else if transtype = "LOGRATIO" then f[1+(i-1)*(r+t):(i*r)+(i-1)*t] = LOG(f[1+(i-
1)*(r+t):(i*r)+(i-1)*t]);
            else if transtype = "INCDENS" then f[1+(i-1)*(2*r+t):(i*2*r)+(i-1)*t] =
LOG(f[1+(i-1)*(2*r+t):(i*2*r)+(i-1)*t]);
         end;
         if transtype = "INCDENS" then do;
            ftemp = J(2*h*(r+t), 1, 0);
            if t = 0 then M = I(r)||-I(r);
            else do;
```

```
               top = I(r)||-I(r)||J(r,t,0);
               bottom = J(t,2*r,0)||I(t);
               M = top // bottom;
               free top bottom;
            end;
            do i = 1 to 2*h;
               ftemp[1+(i-1)*(r+t):i*(r+t)] = M * f[1+(i-1)*(2*r+t):i*(2*r+t)];
            end;
            f = ftemp;
            free ftemp M;
         end;
      finish TRANSF;

****************;
****************;
****************;

      start RANDPARCOV(h, r, t, c, hypoth, f, V, n, varnames, transform, seed, nreps,
combine);
         if t>0 then X = I(r)//J(t,r,0);
         else if t=0 then X = I(r);

         if hypoth = "ALT" then loopcount = nreps + &numobstot + 1;
         else loopcount = nreps + 1;

         twosided = 0;
         one_lower = 0;
         one_upper = 0;

         betasamp = J(loopcount, 1, 0);
         if t > 0 then covxact = 0;

         if combine = 'FIRST' then do;
            do i = 1 to loopcount;
               if (transform = 'LOGISTIC' | transform = 'LOGRATIO') then do;
                  fsub = f[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  Vsub = V[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  run TRANSFORM(h, r, t, fsub, Vsub, hypoth, n[1+(i-1)*2*h:i*2*h], transform);
               end;
               else if transform = 'INCDENS' then do;
                  fsub = f[1+(i-1)*2*h*(2*r+t):i*2*h*(2*r+t),];
                  Vsub = V[1+(i-1)*2*h*(2*r+t):i*2*h*(2*r+t),];
                  run TRANSFORM(h, r, t, fsub, Vsub, hypoth, n[1+(i-1)*2*h:i*2*h], transform);
               end;
               else do;
                  fsub = f[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  Vsub = V[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
               end;

               dh = CREATEDH(h, r, t, fsub);
               Vdh = VARSTRAT(h, r, t, Vsub, n[1+(i-1)*2*h:i*2*h]);
               wh = CREATEWH(h, c, n[1+(i-1)*2*h:i*2*h]);
               Vd = WGTSUM(h, Vdh, wh, 2);
               d = WGTSUM(h, dh, wh, 1);

               betasamp[i] = ESTIMATE(X, Vd, d);
               if i = 1 & t > 0 then covxact0 = (d - X*betasamp[1+(i-1)*r:i*r])`*INV(Vd)*(d -
X*betasamp[1+(i-1)*r:i*r]);
               if (i >= 2) & (i <= (nreps + 1)) then do;
                  twosided = twosided + (abs(betasamp[i]) >= abs(betasamp[1]));
                  one_lower = one_lower + (betasamp[i] <= betasamp[1]);
                  one_upper = one_upper + (betasamp[i] >= betasamp[1]);
                  if t > 0 then covxact = covxact + ((d - X*betasamp[i])`*INV(Vd)*(d -
X*betasamp[i]) >= covxact0);
               end;
            end;
         end;
         else if (combine = 'LAST' | combine = 'NONE') then do;
            if hypoth = "ALT" then do;
               jackmean = J(h, 1, 0);
               jackest = J(&numobstot,1,0);
```

```
               l = 1;
               ntemp = sum(n[1:2]);
               ntot = ntemp;
            end;

            do i = 1 to loopcount;
               betaall = J(h, 1, 0);
               vbetaall = J(h, r, 0);
               if t > 0 then Qxact = 0;

               if (transform = 'LOGISTIC' | transform = 'LOGRATIO') then do;
                  fsub = f[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  Vsub = V[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  run TRANSFORM(h, r, t, fsub, Vsub, hypoth, n[1+(i-1)*2*h:i*2*h], transform);
               end;
               else if transform = 'INCDENS' then do;
                  fsub = f[1+(i-1)*2*h*(2*r+t):i*2*h*(2*r+t),];
                  Vsub = V[1+(i-1)*2*h*(2*r+t):i*2*h*(2*r+t),];
                  run TRANSFORM(h, r, t, fsub, Vsub, hypoth, n[1+(i-1)*2*h:i*2*h], transform);
               end;
               else do;
                  fsub = f[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  Vsub = V[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
               end;

               dh = CREATEDH(h, r, t, fsub);
               Vdh = VARSTRAT(h, r, t, Vsub, n[1+(i-1)*2*h:i*2*h]);

               wh = CREATEWH(h, c, n[1+(i-1)*2*h:i*2*h]);

               do j = 1 to h;
                  VEE = Vdh[1+(j-1)*(r+t):j*(r+t),];
                  dee = dh[1+(j-1)*(r+t):j*(r+t)];
                  betaall[1+(j-1)*r:j*r] = ESTIMATE(X, VEE, dee);
                  vbetaall[1+(j-1)*r:j*r,] = VAREST(X, VEE);

                  if t > 0 then Qxact = Qxact + (dee - X*betaall[1+(j-
1)*r:j*r])`*INV(VEE)*(dee - X*betaall[1+(j-1)*r:j*r]);

                  if hypoth = "ALT" then do;
                     if (j = 1) & (i >= (nreps + 2)) then do;
                        jackest[i-nreps-1] = ESTIMATE(X, VEE, dee);
                        jackmean[l] = jackmean[l] + jackest[i-nreps-1];
                     end;
                  end;
               end;

               if hypoth = "ALT" then do;
                  if i = (nreps + 1 + ntot) then do;
                     jackmean[l] = jackmean[l] / ntemp;
                     l = l + 1;
                     ntemp = sum(n[1+(l-1)*2:2*l]);
                     ntot = ntot + ntemp;
                  end;
               end;

               betasamp[i] = WGTSUM(h, betaall, wh, 1);
               if i = 1 & t > 0 then covxact0 = Qxact;

               if (i >= 2) & (i <= (nreps + 1)) then do;
                  twosided = twosided + (abs(betasamp[i]) >= abs(betasamp[1]));
                  one_lower = one_lower + (betasamp[i] <= betasamp[1]);
                  one_upper = one_upper + (betasamp[i] >= betasamp[1]);
                  if t > 0 then covxact = covxact + (Qxact >= covxact0);
               end;
            end;
         end;
         else if (transform = 'LOGISTIC' | transform = 'LOGRATIO'| transform = 'INCDENS') &
combine = 'PRETRANSFORM' then do;
            if (transform = 'LOGISTIC' | transform = 'LOGRATIO') then do;
               VEE = J(loopcount*2*h*(r+t), r+t, 0);
```

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```
            end;
            else if transform = 'INCDENS' then do;
               VEE = J(loopcount*2*h*(2*r+t), 2*r+t, 0);
            end;
            l = 1;
            do i = 1 to loopcount;
               do j = 1 to 2*h;
                  ntemp = n[1+(i-1)*2*h:i*2*h];
                  if (transform = 'LOGISTIC' | transform = 'LOGRATIO') then do;
                     VEE[1+(l+j-2)*(r+t):(l+j-1)*(r+t),] = V[1+(l+j-2)*(r+t):(l+j-1)*(r+t),] /
ntemp[j];
                  end;
                  else if transform = 'INCDENS' then do;
                     VEE[1+(l+j-2)*(2*r+t):(l+j-1)*(2*r+t),] = V[1+(l+j-2)*(2*r+t):(l+j-
1)*(2*r+t),] / ntemp[j];
                  end;
               end;
               l = l + (2 * h);
            end;

            do i = 1 to loopcount;
               wh = CREATEWH(h, c, n[1+(i-1)*2*h:i*2*h]);
               if (transform = 'LOGISTIC' | transform = 'LOGRATIO') then do;
                  fsub = f[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];
                  Vsub = VEE[1+(i-1)*2*h*(r+t):i*2*h*(r+t),];

                  fstar = WGTSUM2(h, r, t, fsub, wh, 1);
                  Vstar = WGTSUM2(h, r, t, Vsub, wh, 2);
               end;
               else if transform = 'INCDENS' then do;
                  fsub = f[1+(i-1)*2*h*(2*r+t):i*2*h*(2*r+t),];
                  Vsub = VEE[1+(i-1)*2*h*(2*r+t):i*2*h*(2*r+t),];
                  fstar = WGTSUM2(h, 2*r, t, fsub, wh, 1);
                  Vstar = WGTSUM2(h, 2*r, t, Vsub, wh, 2);
               end;

               run TRANSFORM(1, r, t, fstar, Vstar, hypoth, n, transform);
               Vdh = VARSTRAT(1, r, t, Vstar, J(2,1,1));
               dh = CREATEDH(1, r, t, fstar);
               d = WGTSUM(1, dh, 1, 1);
               Vd = WGTSUM(1, Vdh, 1, 2);
               betasamp[i] = ESTIMATE(X, Vd, d);

               if i = 1 & t > 0 then covxact0 = (d - X*betasamp[i])`*INV(Vd)*(d -
X*betasamp[i]);
               if (i >= 2) & (i <= (nreps + 1)) then do;
                  twosided = twosided + (abs(betasamp[i]) >= abs(betasamp[1]));
                  one_lower = one_lower + (betasamp[i] <= betasamp[1]);
                  one_upper = one_upper + (betasamp[i] >= betasamp[1]);
                  if t > 0 then covxact = covxact + ((d - X*betasamp[i])`*INV(Vd)*(d -
X*betasamp[i]) >= covxact0);
               end;
            end;
         end;

         twosided = twosided / nreps;
         one_lower = one_lower / nreps;
         one_upper = one_upper / nreps;
         if t > 0 then covxact = covxact / nreps;

         create _&dsnout._betasamp var{betasamp};
            append;
         close _&dsnout._betasamp;

         if t > 0 then do;
            create _&dsnout._covxact var{covxact};
            append;
            close _&dsnout._covxact;
         end;

         if hypoth = "ALT" & (combine = "FIRST" | combine = "PRETRANSFORM") then do;
```

```
            bias = probit(sum((betasamp[2:(nreps+1)] < betasamp[1]) ) /
nrow(betasamp[2:(nreps+1)]));
            jackmean = sum(betasamp[(nreps+2):nreps+&numobstot+1])/&numobstot;
            accel = sum((betasamp[(nreps+2):nreps+&numobstot+1]-jackmean)##3) /
(6*(sum((betasamp[(nreps+2):nreps+&numobstot+1]-jackmean)##2))**(1.5));
            alpha_low = probnorm(bias + (bias + probit(&alpha/2))/(1-accel*(bias +
probit(&alpha/2))));
            alpha_hi = probnorm(bias + (bias + probit(1-&alpha/2))/(1-accel*(bias + probit(1-
&alpha/2))));
         end;
         else if hypoth = "ALT" & (combine = 'LAST' | combine = 'NONE') then do;
            jackdelta = J(&numobstot,1,0);
            l = 1;
            ntemp = sum(n[1:2]);
            ntot = ntemp;

            do i = (nreps + 2) to (nreps + &numobstot + 1);
               jackdelta[i-nreps-1] = jackest[i-nreps-1] - jackmean[1+(l-1)*r:l*r];

               if i = (nreps + 1 + ntot) then do;
                  l = l + 1;
                  ntemp = sum(n[1+(l-1)*2:2*l]);
                  ntot = ntot + ntemp;
               end;
            end;

            l = 1;
            ntemp = sum(n[1:2]);
            ntot = ntemp;
            jacksum2 = J(r*h,1,0);
            jacksum3 = J(r*h,1,0);
            do i = (nreps + 2) to (nreps + &numobstot + 1);
               jacksum2[l] = jacksum2[l] + jackdelta[i-nreps-1]##2;
               jacksum3[l] = jacksum3[l] + jackdelta[i-nreps-1]##3;

               if i = (nreps + 1 + ntot) then do;
                  l = l + 1;
                  ntemp = sum(n[1+(l-1)*2:2*l]);
                  ntot = ntot + ntemp;
               end;
            end;

            jacktotsum2 = J(r,1,0);
            jacktotsum3 = J(r,1,0);

            do l = 1 to h;
               ntemp = sum(n[1+(l-1)*2:2*l]);
               jacktotsum2 = jacktotsum2 + jacksum2[l] / ntemp##2;
               jacktotsum3 = jacktotsum3 + jacksum3[l] / ntemp##3;
            end;

            bias = probit(sum((betasamp[2:(nreps+1)] < betasamp[1]) ) /
nrow(betasamp[2:(nreps+1)]));
            accel = jacktotsum3 / (6*jacktotsum2##(3/2));
            alpha_low = probnorm(bias + (bias + probit(&alpha/2))/(1-accel*(bias +
probit(&alpha/2))));
            alpha_hi = probnorm(bias + (bias + probit(1-&alpha/2))/(1-accel*(bias + probit(1-
&alpha/2))));
         end;

         type = "EXACT";
         trt1 = "&trt1";
         trt2 = "&trt2";
         outcomes = "&outcomes";
         covariates = "&covars";
         strata = "&strata";
         hypothesis = "&hypoth";
         seed = &seed;
         edit _&dsnout._exact;
            append;
         close _&dsnout._exact;
```

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```
      finish RANDPARCOV;

****************;
****************;
****************;

      use _work_means where(_sample_ = 0);
         read all var{&workoutcomes %if %upcase(&transform) = INCDENS %then %do; &exposures
%end; &covars} into f;
         read all var{_freq_} into n;
      close;
      use _work_covar where(_sample_ = 0);
         read all var{&workoutcomes %if %upcase(&transform) = INCDENS %then %do; &exposures
%end; &covars} into V;
      close;

      f = COLVEC(f);
      varnames = {&workoutcomes &covars}`;
      strat = "%upcase(&strata)";
      combine = "%upcase(&combine)";
      transform = "%upcase(&transform)";
      hypoth = "%upcase(&hypoth)";

      run NPARCOV4(&numstrat, &numresp, &numcov, &c, hypoth, f, V, n, varnames, combine,
transform);

      %if %upcase(&exact) = YES %then %do;
         free f n V;
         use _work_means;
            read all var{&workoutcomes %if %upcase(&transform) = INCDENS %then %do; &exposures
%end; &covars} into f;
            read all var{_freq_} into n;
         close;
         use _work_covar;
            read all var{&workoutcomes %if %upcase(&transform) = INCDENS %then %do; &exposures
%end; &covars} into V;
         close;

         f = COLVEC(f);
         run RANDPARCOV(&numstrat, &numresp, &numcov, &c, hypoth, f, V, n, varnames,
transform, &seed, &nreps, combine);
      %end;
      quit;

      %if &numcov >= 1 %then %do;
         data _&dsnout._covtest(where = (type ne ""));
            set _&dsnout._covtest;
         run;
      %end;

      %if %upcase(&hypoth) = ALT %then %do;
         data _&dsnout._ci(where = (type ne ""));
            set _&dsnout._ci;
         run;
      %end;

      %if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) > 0 and
%upcase(&hypoth) = ALT %then %do;
         data _&dsnout._ratioci(where = (type ne ""));
            set _&dsnout._ratioci;
         run;
      %end;

      %if %index(PODDS, %upcase(&transform)) > 0 %then %do;
         data _&dsnout._homogen(where = (type ne ""));
            set _&dsnout._homogen;
         run;
      %end;

      %if %upcase(&exact) = YES %then %do;
         data _&dsnout._exact(where = (type ne ""));
```

```
            set _&dsnout._exact;
         run;
      %end;

      %if %upcase(&exact) = YES %then %do;
         data _&dsnout._betasamp;
            length flag $ 12;
            set _&dsnout._betasamp;
            if _n_ = 1 then flag = "OBSERVED";
            %if %upcase(&hypoth) = ALT %then %do;
               else if 2 <= _n_ <= %sysevalf(&nreps + 1) then flag = "BOOTSTRAP";
            %end;
            %else %if %upcase(&hypoth) = NULL %then %do;
               else if 2 <= _n_ <= %sysevalf(&nreps + 1) then flag = "PERMUTATION";
            %end;
            %if %upcase(&hypoth) = ALT %then %do;
               else if _n_ > %sysevalf(&nreps + 1) then flag = "JACKKNIFE";
            %end;
         run;

         %if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) %then %do;
            data _&dsnout._betasamp;
               set _&dsnout._betasamp;
               EXPBETASAMP = exp(betasamp);
            run;
         %end;
      %end;

      %if %upcase(&exact) = YES and &numcov >= 1 %then %do;
         data _&dsnout._covtest;
            merge _&dsnout._covtest _&dsnout._covxact;
         run;

         proc datasets nolist;
            delete _&dsnout._covxact;
         quit;
      %end;

      %if %upcase(&exact) = YES and %upcase(&hypoth) = ALT %then %do;
         data _&dsnout._exact;
            set _&dsnout._exact;
            call symput("alpha_low", alpha_low);
            call symput("alpha_hi", alpha_hi);
            drop one_lower one_upper twosided;
         run;

         %PCTCI(flag = BCA, low = %sysevalf(&alpha_low * 100), hi = %sysevalf(&alpha_hi *
100));

         %PCTCI(flag = PCT, low = %sysevalf(&alpha/2 * 100), hi = %sysevalf((1 - &alpha/2) *
100));

         data _&dsnout._exact;
            merge _&dsnout._exact
                  _&dsnout._pctfinal
                  _&dsnout._bcafinal;
            %if %index(LOGISTIC PODDS LOGRATIO INCDENS, %upcase(&transform)) %then %do;
               bca_ratio_lower = exp(bca_lower);
               bca_ratio_upper = exp(bca_upper);
               pct_ratio_lower = exp(pct_lower);
               pct_ratio_upper = exp(pct_upper);
            %end;
         run;

         data _&dsnout._covtest;
            set _&dsnout._covtest;
            drop covxact;
         run;

         proc datasets nolist;
            delete _&dsnout._bcafinal _&dsnout._pctfinal;
```

```
         quit;
      %end;

      data _&dsnout._covbeta;
         length type $ 10;
         set _&dsnout._covbeta;
         type = "COVBETA";
      run;

      proc datasets nolist;
         delete _WORK_MEANS _WORK_COVAR _WORK_TEMP _WORK_NSTRT _WORK_NTRTS _WORK_NTRTS_CHK
_WORK_OUTSAMP _WORK_JACK;
      quit;

      %if %upcase(&details) = YES %then %do;
         proc datasets;
         quit;
      %end;

      data _&dsnout._deptest(where = (type ne ""));
         set _&dsnout._deptest;
      run;

      ods results;
   %stopmac:;
%mend NPARCOV4;

****************;
****************;
****************;

%macro PCTCI(flag = BCA, low = %sysevalf(&alpha_low * 100), hi = %sysevalf(&alpha_hi * 100));
   proc univariate noprint data = _&dsnout._betasamp;
      var betasamp;
      output out = _&dsnout._&flag.final pctlpts = &low &hi pctlpre = &flag._;
      where flag = "BOOTSTRAP";
   run;

   proc transpose data = _&dsnout._&flag.final out = _&dsnout._&flag.final;
   run;

   data _&dsnout._&flag.final;
      set _&dsnout._&flag.final;
      if _n_ = 1 then ci = "&flag._LOWER";
      else ci = "&flag._UPPER";
   run;

   proc transpose data = _&dsnout._&flag.final out = _&dsnout._&flag.final(drop = _name_);
      var col1;
      id ci;
   run;
%mend PCTCI;

****************;
****************;
****************;

%macro MISSDAT(varlist = , data = );
   data _work_miss;
      set &data;
      totmiss = nmiss(of &varlist);
   run;

   proc means sum noprint data = _work_miss;
      var totmiss;
      output out = _work_miss(drop = _TYPE_ _FREQ_) sum = sum;
   run;

   data _null_;
      set _work_miss;
      call symput('missind', trim(left(put(sum,8.))));
```

```
   run;

   proc datasets nolist;
      delete _work_miss;
   quit;
%mend MISSDAT;

*****************;
*****************;
*****************;

%macro SURVSCORE(eventlist = , timelist = , score = %str(LOGRANK));
   %do sloop = 1 %to &numresp;
      %let event = %scan(&eventlist, &sloop);
      %let time = %scan(&timelist, &sloop);

      proc freq noprint data = _work_temp;
         tables &time * &event / out = _work_surv(drop = percent);
      run;

      proc means n noprint data = _work_temp;
         var &time;
         output out = _work_tot(drop = _freq_ _type_) n = total;
      run;

      proc sort data = _work_surv out = _work_surv;
         by &time descending &event;
      run;

      %if &score = LOGRANK %then %do;
         data _work_surv;
            set _work_surv;
            if _n_ = 1 then set _work_tot;
            ratio = 0;
            retain survscore cumsum atrisk cumratio;
            if _n_ = 1 then cumsum = count;
            else cumsum = cumsum + count;
            if &event = 1 then do;
               atrisk = total - cumsum + count;
               ratio = count / atrisk;
            end;
            if _n_ = 1 then cumratio = ratio;
            else cumratio = cumratio + ratio;
            if _n_ = 1 and &event = 0 then survscore = 0;
            else do;
               if &event = 1 then survscore = 1 - cumratio;
               else if &event = 0 then survscore = - cumratio;
            end;
            keep &time &event count total survscore;
         run;
      %end;
      %else %if &score = WILCOXON %then %do;
         data _work_surv;
            set _work_surv;
            if _n_ = 1 then set _work_tot;
            ratio = 1;
            retain survscore cumsum atrisk cumratio;
            if _n_ = 1 then cumsum = count;
            else cumsum = cumsum + count;
            if &event = 1 then do;
               atrisk = total - cumsum + count;
               ratio = (atrisk - count) / atrisk;
            end;
            if _n_ = 1 then cumratio = ratio;
            else cumratio = cumratio * ratio;
            if _n_ = 1 and &event = 0 then survscore = 0;
            else do;
               if &event = 1 then survscore = 2 * cumratio - 1;
               else if &event = 0 then survscore = cumratio - 1;
            end;
            keep &time &event count total survscore;
```

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```
         run;
      %end;

      proc sort data = _work_temp;
         by &time descending &event;
      run;

      data _work_temp;
         merge _work_temp _work_surv(keep = &time &event survscore rename = (survscore =
&score._&event));
         by &time descending &event;
      run;

      data _&dsnout._surv;
         set _work_temp;
         %if &numstrat = 1 %then %do;
            drop _NONE;
         %end;
      run;
   %end;
%mend SURVSCORE;
```

[redacted]

Statistical Analysis Plan for Interventional Studies

Addendum 1

Sponsor Name: Zambon SpA

Protocol Number: Z7224L01 (Promis I)

Protocol Title: A double-blind, placebo-controlled, multi-centre, clinical trial to investigate the efficacy and safety of 12 months of therapy with inhaled colistimethate sodium in the treatment of subjects with non-cystic fibrosis bronchiectasis chronically infected with *Pseudomonas aeruginosa* (*P. aeruginosa*)

Protocol Version and Date: (DD-Mmm-YYYY): Final Version 7.0 dated 22-Oct-2019

[redacted] **Project Code:** [redacted]

Author: [redacted], Principal Biostatistician

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	22-Jul-2021	PPD	Initial Release Version

I confirm that I have reviewed this document and agree with the content.

Approvals

CCI Approval

PPD, Principal Biostatistician	PPD	Electronically signed by: PPD Reason: I am the author Date: Jul 22, 2021 15:00 GMT+1 22-Jul-2021
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD, Director, Biostatistics	PPD	Electronically signed by: PPD Reason: I am the reviewer Date: Jul 22, 2021 15:08 GMT+1 22-Jul-2021
Name, Title Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

Zambon SpA Approval

PPD, Clinical Development Program Head for NCFB	PPD	Electronically signed by: PPD Reason: I am the approver Date: Jul 22, 2021 15:10 GMT+1 22-Jul-2021
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD, Clinical Research Consultant	PPD	Electronically signed by: PPD Reason: I am the reviewer Date: Jul 22, 2021 10:04 EDT 22-Jul-2021
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
CFU	Colony Forming Units
CI	Confidence Interval
CR	Copy Reference
MAR	Missing At Random
mITT	Modified Intention-To-Treat
NCFB	Non-Cystic Fibrosis Bronchiectasis
P. aeruginosa	*Pseudomonas aeruginosa*
SAP	Statistical Analysis Plan
SD	Standard Deviation
CCI [redacted]	CCI [redacted]
SOP	Standard Operating Procedure

2. Purpose

The purpose of this Statistical Analysis Plan (SAP) Addendum is to ensure that the post-hoc CCI [redacted] analyses (which will be produced to demonstrate that the positive results obtained from the primary analysis of the study are reproducible) and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This document serves as an Addendum to the Final SAP v2.0 dated 8th April 2021.

2.1. Responsibilities

CCI [redacted] will perform the post-hoc statistical CCI [redacted] analyses and are responsible for the production and quality control of all tables and figures described in this document.

2.2. Timings of Analyses

The primary analysis of safety and efficacy, as planned in the Final SAP v2.0 dated 8th April 2021, was conducted after all subjects had completed the final study visit or terminated early from the study. At the time of writing, the clinical database has been locked, the study has been formally unblinded, and therefore the post-hoc CCI [redacted] analyses planned in this Addendum will be conducted after the primary analysis has been completed.

3. Study Objectives

Refer to Section 2 of the Final SAP v2.0 dated 8th April 2021 for the primary objectives of the trial.

The objectives of the post-hoc CCI [redacted] analyses planned in this Addendum are:

- To demonstrate reproducibility of the positive results observed in the primary analysis, by means of assessing treatment interactions with various factors to examine whether the treatment effect is the same at each level of those factors;
- To check internal consistency of study results, as is required for regulatory applications based on one single pivotal study.

4. Endpoints

Refer to Sections 2.1 and 2.2 of the Final SAP v2.0 dated 8th April 2021 for details of the primary and secondary efficacy endpoints, respectively.

5. Analysis Populations

Refer to Section 3.5 of the Final SAP v2.0 dated 8th April 2021 for definitions of all populations used for the primary analysis. All outputs planned under this Addendum will be based on the modified Intention-To-Treat (mITT) Population, as defined in Section 3.5.2 of the Final SAP v2.0 dated 8th April 2021.

6. Efficacy

6.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint for this trial is the mean annual non-cystic fibrosis bronchiectasis (NCFB) pulmonary exacerbation rate, defined in detail in Section 4.7.1 of the Final SAP v2.0 dated 8th April 2021. The primary efficacy analysis was conducted using a negative binomial model including treatment, country and use of stable concomitant therapy with oral macrolides (Yes; No) as fixed effects and log-time on treatment as an offset. The planning of this analysis is described in Section 4.7.4 of the Final SAP v2.0 dated 8th April 2021.

This section describes the post-hoc [redacted] analyses intended to assess the degree of internal consistency of the overall trial primary efficacy endpoint analysis results across a range of baseline and prognostic factors.

The confidence intervals (CIs) of the adjusted mean pulmonary exacerbation rates according to the primary efficacy analysis were very wide (<0.001, >9999.999) in both the Colistimethate Sodium and Placebo groups. This is caused by the inclusion of country as an effect in the model, due to some countries having very few subjects, resulting in large standard errors. The negative binomial model used for the primary efficacy analysis will be repeated without the country covariate included, in order to obtain more robust CIs for the adjusted mean pulmonary exacerbation rates in each treatment group, and to demonstrate that those means are stable. The adjusted mean annual NCFB pulmonary exacerbation rates in each treatment group and the adjusted rate ratio with their 95% CIs will be estimated by the model. The number of subjects considered in the model will be provided by treatment group. P-values of the stable concomitant therapy with oral macrolides effect based on Wald chi-square test will also be presented.

6.1.1. [redacted] Analysis for Discontinuers

[redacted] analyses based on multiple imputation (using the approach proposed by Keene et al. [1]), where the number of NCFB pulmonary exacerbations from the end of the follow-up period up to day 365 were imputed for subjects with a follow-up duration shorter than 365 days, were conducted on the primary model using both Missing At Random (MAR) and Copy Reference (CR) imputation strategies, as planned in Section 4.7.4.2 of the Final SAP v2.0 dated 8th April 2021.

As the MAR imputation demonstrated a significantly lower annual NCFB pulmonary exacerbation rate for subjects in the Colistimethate Sodium group compared to the Placebo group, with that significance being lost using CR imputation, it is pertinent to perform a tipping point analysis to determine the scenario where the treatment effect in subjects with missing data overturns the significant treatment effect obtained in the MAR analysis.

Missing NCFB pulmonary exacerbation counts for each subject will be imputed similarly to the MAR approach, with the imputed number of exacerbations based on the Bayesian posterior sample for each imputation in the Colistimethate Sodium group being increased according to a shift parameter, δ (delta, as described by Akacha and Ogundimu [2]), where δ will be varied from 0 to 1 in increments of 0.01. That is, the mean imputed number of pulmonary exacerbations based on the Bayesian posterior sample will be increased in increments of 1%, starting at the initial value from the MAR approach (0%) up to 100%, where a 100% increase equates to the mean imputed number of pulmonary exacerbations being doubled in the Colistimethate Sodium group.

As for the MAR and CR analyses already conducted, the imputation model for the tipping point analysis will include treatment, pooled site, and use of stable concomitant therapy with oral macrolides (Yes; No), and one thousand imputations will be performed for each value of δ. Analysis of the total number of NCFB pulmonary exacerbations (observed + imputed events) will be based on the same negative binomial model used for the primary efficacy analysis. Estimates from the models will then be combined using Rubin's rule [3] for each value of δ.

The number of subjects considered in the model in each treatment group will be presented. The value of δ at which the conclusion changes from favourable to unfavourable (i.e. where the p-value increases to above 0.05; that is, where the imputed number of pulmonary exacerbations in the Colistimethate Sodium group has to increase by 100δ% for statistical significance to be lost) will be presented, along with the smallest value of δ for which the p-value remains below 0.05.

For each of these 2 values of δ, the adjusted mean NCFB pulmonary exacerbation rates and 95% CIs in each treatment group, the adjusted rate ratio and 95% CI, and the p-value from the multiple imputation analysis using that value of δ will also be presented.

6.1.2. CCI **Analyses with Additional Covariates and Interactions**

In order to explore the statistical evidence for the degree of consistency of treatment effect at each level of a given prognostic factor, the negative binomial model used for the primary analysis will be repeated with the following additional effects included (one model per bullet point below):

- Country-by-treatment interaction;
- Number of NCFB pulmonary exacerbations requiring oral or intravenous antibiotics in the 12 months prior to study entry (# exacerbations) (1; 2; >2) and # exacerbations-by-treatment interaction;
- Previous usage of colistimethate sodium/colistin (Yes; No) and previous usage-by-treatment interaction;

- Age (as a continuous covariate) and age-by-treatment interaction;
- Age group (<65 years; >=65 years) and age group-by-treatment interaction;
- Gender (Female; Male) and gender-by-treatment interaction.

As was done for the primary analysis, the adjusted mean annual NCFB pulmonary exacerbation rates in each treatment group and the adjusted rate ratio with their 95% CIs will be estimated by the model. The number of subjects considered in the model will be provided by treatment group. P-values of the effects and interactions based on Wald chi-square test will also be presented.

6.1.3. [redacted] Analyses by Subgroup

The primary model was already fitted separately for each country, for each # exacerbations (1; 2; >2), and for each previous usage of colistimethate sodium/colistin (Yes; No) category, as planned in Sections 4.7.4, 4.7.4.5 and 4.7.4.6, respectively, of the Final SAP v2.0 dated 8th April 2021.

The NCFB pulmonary exacerbation rate ratios and their corresponding 95% CIs will be presented on a forest plot overall and for each country, and overall and for each # exacerbations (1; 2; >2), respectively. It is known from the analysis previously conducted, that exacerbation rate ratios are not calculable for Belgium, Netherlands and Switzerland due to lack of treated subjects in those countries. These countries will, therefore, not be shown on the forest plot.

In order to have a complete breakdown of the primary model for all factors considered, the primary model will be fitted separately for each of the following groups:

- Age group (<65 years; >=65 years);
- Gender (Female; Male).

For consistency with the subgroup analyses already conducted, p-values will be presented for adjusted rate ratios, CIs and model effects. However, it should be noted that the study is not powered for subgroup analyses; what is more of interest is the estimate of the treatment effect at each level of each factor.

6.2. Secondary Efficacy Endpoints and Analyses

6.2.1. [redacted]

The change from baseline to Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 in [redacted], as defined in Section 4.7.6.2 of the Final SAP v2.0 dated 8th April 2021, will be displayed on a line plot for each treatment group. The mean change from baseline +/- standard deviation (SD) will be presented for each treatment at each visit.

6.2.2. [redacted]

The change from Baseline to Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7 in [redacted], as defined in Section 4.7.6.3 of the Final SAP v2.0 dated 8th April 2021, will be displayed on a line plot for each treatment group. The mean change from baseline +/- SD will be presented for each treatment at each visit.

7. Reference List

1. Keene, O. N., Roger, J. H., Hartley, B. F. and Kenward, M. G., Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical Statistics 2014; 13: 258-264
2. Akacha, M. and Ogundimu, E. O., Sensitivity analyses for partially observed recurrent event data. Pharmaceutical Statistics 2016; 15: 4-14
3. Barnard, J and Rubin, D. B., Small-sample degrees of freedom with multiple imputation. Biometrika 1999; 86: 948-955

8. Programming Considerations

Refer to Sections 5.1 and 5.2 of the Final SAP v2.0 dated 8th April 2021 for details of the formatting and display conventions to be followed for all tables and figures planned under this SAP Addendum.

9. Quality Control

SAS programs will be developed to produce output such as analysis data sets, summary tables, figures or statistical analyses. An overview of the development of programs is detailed in the [redacted] Developing Statistical Programs Standard Operating Procedure (SOP) (3907).

[redacted] SOPs Developing Statistical Programs (3907), Conducting the Transfer of Biostatistical Deliverables (3908) and the study-specific SAS Programming and Validation Plan Final v1.0 dated 23rd March 2020, describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce correct and accurate output by checking for their logic, efficiency and commenting and by review of the produced output.

10. Index of Tables

Table Number	Name	Analysis Set
14.2.1.1.1.2	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Including Country-by-Treatment Interaction	(mITT Population)
14.2.1.1.1.3	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Excluding Country Covariate	(mITT Population)
14.2.1.1.4.1	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - Tipping Point Analysis	(mITT Population)
14.2.1.1.7.1	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Including Number of Pulmonary Exacerbations Requiring Oral or Intravenous Antibiotics in the 12 Months Prior to Study Entry and by-Treatment Interaction	(mITT Population)
14.2.1.1.8.1	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Including Previous Usage of Colistimethate Sodium/Colistin and by-Treatment Interaction	(mITT Population)
14.2.1.1.9.1	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Including Age as Covariate and by-Treatment Interaction	(mITT Population)

Table Number	**Name**	**Analysis Set**
14.2.1.1.9.2	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Including Age Group and by-Treatment Interaction	(mITT Population)
14.2.1.1.9.3	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model by Age Group	(mITT Population)
14.2.1.1.10.1	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model Including Gender and by-Treatment Interaction	(mITT Population)
14.2.1.1.10.2	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model by Gender	(mITT Population)

11. Index of Figures

Figure Number	**Name**	**Analysis Set**
14.2.1.1.1.4	Forest Plot for Rate Ratio (Colistimethate Sodium versus Placebo) of NCFB Pulmonary Exacerbations by Country	(mITT Population)
14.2.1.1.7.2	Forest Plot for Rate Ratio (Colistimethate Sodium versus Placebo) of NCFB Pulmonary Exacerbations by Number of Pulmonary Exacerbations Requiring Oral or Intravenous Antibiotics in the 12 Months Prior to Study Entry	(mITT Population)
14.2.2.5.5	Change from Baseline in CCI by Visit	(mITT Population)
14.2.2.6.3	Change from Baseline in CCI by Visit	(mITT Population)

[redacted]	**Note to File**

Project /Protocol No.	[redacted]/Z7224L01 (Promis I)
Date:	09-Mar-2021 Correction: should be 09-Mar-2022 [redacted] [redacted]
CC:	[redacted] (Zambon SpA), [redacted] (Zambon SpA), [redacted] (Zambon SpA), [redacted] (Zambon SpA) [redacted] [redacted] [redacted] TMF

RE: Additional Statistical Analyses Using Grouped Countries

As detailed in the Statistical Analysis Plan (SAP) Final Version 2.0 dated 08-Apr-2021, the statistical modelling included country as a fixed effect. Due to certain countries having low numbers of subjects and consequentially low degrees of freedom and elevated standard errors, the confidence intervals (CIs) for the treatment least square (LS) mean pulmonary exacerbation rates were extremely wide.

To demonstrate the robustness of the primary endpoint, below additional analysis were performed:

- ADSL dataset update to add the variable for grouped country
- Generation of a new table (Table 14.2.1.1.1.5), repeating the primary efficacy analysis with grouped country in place of original country.
- Generattion of a new table (Table 14.2.1.1.4.2), repeating the missing-at-random and copy-reference [redacted] analyses of the primary endpoint with grouped country in place of original country. A single dispersion parameter common to both treatment groups will be used.
- Generation of a new table (Table 14.2.1.1.4.3), repeating the tipping point analysis of the primary endpoint with grouped country in place of original country. A single dispersion parameter common to both treatment groups will be used.

New Tables generated:

TFL Number	TFL Title
Table 14.2.1.1.1.5	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model with Small Countries Grouped Together (mITT Population)
Table 14.2.1.1.4.2	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - [redacted] Analysis for Discontinuers with Small Countries Grouped Together (mITT Population)
Table 14.2.1.1.4.3	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - Tipping Point Analysis with Small Countries Grouped Together (mITT Population)

As for this additional analysis only the programming and validation for the ADSL ADaM dataset to incorporate the new grouped country variable will be rerun, a SAS PROC COMPARE will be conducted of the updated ADSL dataset against the previously validated version of that dataset, to show that the changes are as expected (i.e. that the only difference is the addition of grouped country, and all other variables in the dataset are identical to the previously validated version). The Analysis Data Reviewer's Guide will be updated to include an explanation of why the dates of ADaM datasets do not run chronologically.

In addition, 2 tables of the 137 TLFs covered by SAP Final Version 2.0 dated 08-Apr-2021 and SAP Addendum 1 Final Version 1.0 dated 22-Jul-2021 will be rerun in order to correct a double-counting issue, (Table 14.2.1.1.4 and Table 14.2.1.1.4.1). The use of individual (ungrouped) countries, and a single dispersion parameter common to both treatment groups, will be maintained in these tables.

TFL Number	TFL Title
Table 14.2.1.1.4	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - CCI Analysis for Discontinuers (mITT Population)
Table 14.2.1.1.4.1	NCFB Pulmonary Exacerbations: Mean Annual Rate by Negative Binomial Model - Tipping Point Analysis (mITT Population)

Created by:

PPD Principal Biostatistician, CCI	PPD	Electronically signed by: PPD Reason: I am the author Date: Apr 5, 2022 11:56 GMT+1	05-Apr-2022
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Reviewed by:

PPD Director Biostatistics, CCI	PPD	Electronically signed by: PPD Reason: I am the reviewer Date: Apr 5, 2022 11:57 GMT+1	05-Apr-2022
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PPD Senior Project Director, CCI	PPD	Electronically signed by: PPD Reason: I am the approver Date: Apr 5, 2022 18:03 GMT+2	05-Apr-2022
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PPD, Clinical Development Head for NCFB, Zambon SpA	PPD	Electronically signed by: PPD Reason: I am the reviewer Date: Apr 5, 2022 12:01 GMT+1	05-Apr-2022
Printed Name, Title	Signature		Date (DD-Mmm-YYYY)
PPD, Head of Scientific Operations, Zambon SpA	PPD	Electronically signed by: PPD Reason: I am the approver Date: Apr 5, 2022 13:57 GMT+2	05-Apr-2022
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