CLINICAL TRIAL PROTOCOL

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 Code Z7224L01

Protocol Name PROMIS I

EudraCT Number 2015-002743-33

Final Date 22 Oct 2019

Version Final 7.0

Zambon SpA
Via Lillo del Duca 10
20091 Bresso - Milan – Italy

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*)

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Author: PPD, Zambon S.p.A.

Sponsor Name and Address: Zambon S.p.A.
Via Lillo del Duca 10
20091 Bresso - Milan – Italy

As agreed and approved by:

PPD

23/10/2019

Date (dd/mm/YYYY) **Dr. PPD, Open R&D Global Head** **SIGNATURE**

PPD

23/oct/2019

Date (dd/mm/YYYY) **PPD, Clinical Development Manager/Project Lead** **SIGNATURE**

ZAMBON CONTACT DETAILS

Zambon S.p.A
Via Lillo del Duca 10
20091 Bresso - Milan (Italy)
Phone: +39 02 665241
Email: clinicaltrials@zambongroup.com

Role	Name	Contact Data
Medical Advisor	PPD	PPD PPD

CONTRACT RESEARCH ORGANISATION CONTACT DETAILS

CCI
United States of America
CCI

Role	Name	Contact Data
Medical Monitor	PPD PPD	PPD PPD
Contact for serious adverse event/pregnancy reporting	CCI	CCI

OTHER INSTITUTIONS

Role	Name	Contact Data
Central Laboratory	CCI	CCI The Netherlands CCI CCI Singapore CCI
Electronic Patient Reported Outcome (eCOA)	CCI	CCI United Kingdom CCI CCI United States of America CCI
Interactive Web Response System (IWRS)	CCI	CCI Belgium CCI
Electronic Data Capture	CCI	CCI United Kingdom PPD
Investigational Medicinal Product (IMP) Packaging and Labelling; Logistics	CCI	CCI United Kingdom. CCI CCI Singapore, CCI

Role	Name	Contact Data
CCI nebuliser and CCI Software	CCI	CCI United Kingdom CCI
CCI data analyser/I-CCI software	CCI	CCI West Sussex CCI

LIST OF COMMITTEES

Not applicable.

SUMMARY OF CHANGE HISTORY

Protocol Version	Key Changes
Protocol Version Final v.4.0; 18 Nov 2016	The Protocol Versions from 1.0 to 3.0 were internal versions and were not submitted. Version 4.0 is the final version that was submitted to CAs in Europe.
Protocol version Final v 4.1: 31 Jan 2017 (UK only)	Amendment made to reflect changes requested by The East of England – Cambridge East Research Ethics Committee 1. Section 8.2.2: detail on the need for contraceptive precautions/use of condoms/not taking part in sperm donation for male participants with female partners of child-bearing potential was added. 2. Section 17.10: a longer follow-up period for pregnancy outcomes was added.
Protocol Version Final v.4.1; 03 July 2017 (Portugal only)	After the revision of the protocol by the CA in Portugal two sections of the protocol (Summary: Exclusion Criteria and Section 8.2.2 Exclusion Criteria) were modified to accommodate the request to adequately characterize the "severe cardiovascular disease" to be considered.
Protocol Version Final v.5.0; 17 April 2018	Global harmonization: protocol revised to harmonize the changes requested by EU EC/CAs and the second pivotal Phase 3 protocol (PROMIS II) following requests received from the US Food and Drug Administration (FDA) in particular regarding the endpoints and statistical analysis. The primary endpoint was amended to two co-primary endpoints of frequency of pulmonary exacerbations and number of exacerbation-free days, with a subsequent increase in sample size and number of countries/sites. Other comments were addressed and the opportunity has been taken to standardize and re-format sections accordingly. In addition, any ambiguities in the text were amended for clarification purposes.
Protocol Version Final v.6.0; 11 Dec 2018	Protocol modified following agreement with the FDA during a Type C Meeting held on 31 Oct 2018 to revert to a single primary endpoint of frequency of pulmonary exacerbations, with CCI [redacted] being included as a secondary endpoint, and (for Promis II) reducing the duration of the treatment period to 12 months. For additional information, please refer to the Summary of Key Changes document associated with this protocol version.
Protocol Version Final v.7.0; 22 Oct 2019	Amendment to reflect the transition in Contract Research Organisation from CCI [redacted] to CCI [redacted] and amending the contact details accordingly. For additional information, including amendments to clarify inclusion and exclusion criteria, please refer to the Summary of Key Changes document associated with this protocol version.

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1. ABBREVIATIONS

CCI	[redacted]
ABPA	Allergic bronchopulmonary aspergillosis
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CA	Competent authority
CBA	Colistin Base Activity
CF	Cystic fibrosis
CFU	Colony forming units
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organisation
CT	Computerised tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eCOA	Electronic clinical outcome assessment
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FOE	Frequency Of Exacerbation
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl transferase
GLI	Global Lung Function Initiative reference equations
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HRCT	High-resolution Computerised Tomography
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
ITT	Intention-to-treat
IU	International Unit
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities

MIC	Minimum Inhibitory Concentration
mITT	modified Intention-to-treat
MIU	Million International Unit
NCFB	*Non-CF-Bronchiectasis*
NTM	Non-Tuberculous Mycobacterial
P. aeruginosa	*Pseudomonas aeruginosa*
PP	Per-protocol population
Q2	Quarter two
Q4	Quarter four
CCI [redacted]	[redacted]
[redacted]	[redacted]
RAN	Randomised population
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
CCI [redacted]	[redacted]
SmPC	Summary of product characteristics
SOPs	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TMF	Trial master file
WHO-DD	World Health Organization-Drug Dictionary

2. SUMMARY

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 Code/Name:	Z7224L01/Promis I
Eudract Number:	2015-002743-33
Phase:	III
Test Product:	Colistimethate sodium (Promixin®/Tadim®) – powder for nebuliser solution vials. Powder 1 million IU (approximately equivalent to 80 mg of colistimethate sodium/33 mg colistin base activity); vehicle 0.45% sodium chloride (saline) solution.
Control Product/Placebo:	Matching vial and 0.45% sodium chloride (saline) solution.
Dosage:	Subjects will administer the investigational medicinal product (IMP) twice daily (morning and evening) via the CCI CCI Aerosol Delivery CCI System. The content of the vial is reconstituted with 1 mL of 0.45% sodium chloride (saline) solution and 1 mL of the medication placed in the CCI device to fill the 0.3 mL nebulisation chamber to give a delivered dose of 10 mg colistin base activity (CBA).
Objective:	The primary objective of the trial is to investigate the effect of the use of inhaled colistimethate sodium, administered twice daily via the CCI for 12 months, compared to placebo in subjects with non–cystic fibrosis bronchiectasis (NCFB) chronically infected with *P. aeruginosa* on the frequency of pulmonary exacerbations. Key secondary objectives are: CCI [redacted]
Design:	Randomised, multi-centre, double-blind, placebo-controlled, parallel group trial. Subjects will be randomised to active or placebo in a 1:1 ratio. The study will consist of a total of 7 clinic visits with a follow-up phone call two weeks after discontinuation of treatment. Additional clinic visits, where feasible, and weekly phone calls will be conducted following pulmonary exacerbations until resolution.
Number of patients:	A total of 420 patients will be randomised to have 340 completed patients (170 for each treatment group).
Trial duration:	First subject in to last subject out: Q2 2017 to Q4 2020, inclusive.
Duration of patient participation:	Screening period up to 30 days, followed by 12 months treatment duration and a follow-up phone call two weeks after discontinuation of treatment.
Participation Countries:	Number of estimated countries: 15
Number of Sites:	Approximately 100
Sample Size:	A total of 420 randomised patients (210 per group) is foreseen assuming a withdrawal rate of approximately 20%, to achieve a total number of completed patients of 170 per group. For the primary endpoint of frequency of exacerbation (FOE), and a Poisson regression allowing for over-dispersion for FOE, with a two-sided significance level of 0.05, a treatment effect of 35% and a follow-up time of 1 year, with an FOE of 1.09 in the placebo group, this sample size will provide a power of 90%.

	If the treatment difference effect size is 30% between the colistimethate sodium and placebo groups, the power with 170 completed patients per group will be 80%.
Population:	Inclusion Criteria: Subjects are eligible if they: 1. are able and willing to give informed consent following a detailed explanation of participation in the protocol and signed consent obtained; 2. are aged 18 years or older of either gender; 3. are diagnosed with NCFB by computerised tomography (CT) or high resolution CT (HRCT) as recorded in the subject's notes and this is their predominant condition being treated; 4. had at least 2 NCFB pulmonary exacerbations requiring oral or inhaled antibiotics or 1 NCFB pulmonary exacerbation requiring intravenous antibiotics in the 12 months preceding the Screening Visit (Visit 1) and had no NCFB pulmonary exacerbation with or without treatment during the period between Visit 1 and Visit 2; 5. have a documented history of *P. aeruginosa* infection; 6. are clinically stable and have not required a change in pulmonary treatment for at least 30 days before the Screening Visit (Visit 1); 7. have pre-bronchodilator FEV_1 ≥25% of predicted; 8. had a positive sputum culture for *P. aeruginosa* from an adequate sample taken at the Screening Visit (Visit 1) or during the screening period. Exclusion Criteria: Subjects are not eligible if they have/are: 1. known bronchiectasis as a consequence of cystic fibrosis (CF); 2. known history of hypogammaglobulinaemia requiring treatment with immunoglobulin, unless fully replaced and considered immuno-competent by the Investigator; 3. myasthenia gravis or porphyria; 4. severe cardiovascular disease such as severe uncontrolled hypertension, ischaemic heart disease or cardiac arrhythmia and any other conditions that would confound the evaluation of safety, in the opinion of the Investigator; 5. had major surgery in the 3 months prior to the Screening Visit (Visit 1) or planned inpatient major surgery during the study period; 6. receiving treatment for allergic bronchopulmonary aspergillosis (ABPA); 7. had massive haemoptysis (greater than or equal to 300 mL or requiring blood transfusion) in the preceding 4 weeks before the Screening Visit (Visit 1) or between Visit 1 and Visit 2; 8. respiratory failure that would compromise patient safety or confound the evaluation of safety or efficacy of the study in the opinion of the Investigator; 9. current active malignancy, except for basal cell carcinoma or squamous cell carcinoma of the skin without metastases; 10. taking immunosuppressive medications (such as azathioprine, cyclosporine, tacrolimus, sirolimus, mycophenolate, rituximab), and/or anti-cytokine medications (such as anti-IL-6 and anti-tumour alpha necrosis factor products) in the preceding year before the Screening Visit (Visit 1); 11. known history of human immunodeficiency virus (HIV); 12. current treatment for non-tuberculous mycobacterial (NTM) lung disease or tuberculosis; 13. known or suspected to be allergic or unable to tolerate colistimethate sodium (intravenous or inhaled) or other polymixins, including previous evidence of bronchial hyper-reactivity following inhaled colistimethate sodium;

14. treatment with long term (≥ 30 days) prednisone at a dose greater than 15 mg a day (or equivalent dose of any other corticosteroid) within 6 months of the Screening Visit 1 (Visit 1);
15. new maintenance treatment with any oral macrolides (e.g. azithromycin/erythromycin/clarithromycin) started within 30 days of the Screening Visit (Visit 1) or started between Visit 1 and Visit 2;
16. use of any intravenous or intramuscular or oral or inhaled anti-pseudomonal antibiotic (except chronic oral macrolide treatment with a stable dose) within 30 days prior to the Screening Visit (Visit 1) and between Visit 1 and Visit 2;
17. pregnant or breast feeding or plan to become pregnant over the next year or of child-bearing potential and unwilling to use a reliable method of contraception for at least one month before randomisation and throughout their involvement in the trial;
18. significant abnormality in clinical evaluations and/or laboratory tests (physical examination, vital signs, haematology, clinical chemistry, clinically relevant impaired renal function, defined as serum creatinine levels ≥2.0x upper limit of normal, ECG) endangering the safe participation of the patient in the study at the Screening Visit (Visit 1) and during the study;
19. participated in another investigational, interventional trial within 30 days prior to the Screening Visit (Visit 1);
20. in the opinion of the Investigator not suitable for inclusion for whatever reason.

Outcome measures:

Primary Efficacy Variable:

Mean annual pulmonary exacerbation rate.

Secondary Efficacy Variables:

- CCI [redacted]

Safety Variables:

- incidence of treatment emergent adverse events (TEAEs);
- absolute changes in percent-predicted FEV_1 from baseline to each post-baseline visit;
- number of subjects experiencing bronchospasm clinically or spirometrically determined following IMP administration;
- CCI [redacted] as determined by *in-vitro* CCI [redacted] from Screening/Randomisation (Visit 1/Visit 2) to Visits 3, 5 and end of treatment (Visit 7) as well as on CCI [redacted] from Exacerbation Visits and clinic visits due to pneumonia;

	• 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.
Statistical Analysis	Primary analyses will be performed on the modified intention-to-treat (mITT) population with exclusions from the ITT defined and justified in the Statistical Analysis Plan (SAP). A supportive analysis will be conducted using a per-protocol (PP) population excluding subjects with major protocol deviations. Annual pulmonary exacerbation rates will be compared between treatment groups using a Poisson regression model allowing for over-dispersion and also considering pooled site, use of stable concomitant therapy with oral macrolides and pulmonary exacerbation frequency in the 12 months preceding Visit 2 as covariates. The primary analyses detailed above will be a comparison of colistimethate sodium against placebo at the end of the 12-month, double-blind phase. Full details will be provided in the SAP. The secondary variable of the CCI will be analysed using a log-rank test comparing two survival curves. The number of CCI will be analysed using an appropriate non-parametric test. The number of CCI will also be analysed using a binomial regression model. The absolute changes in CCI $_1$ and the CCI will be presented separately. scores CCI will be analysed using linear mixed models. An analysis of covariance model on $\log_{10}$ transformed values fitting baselines will be used to compare CCI between treatment groups.

3. INTRODUCTION AND RATIONALE

Background

Bronchiectasis is a debilitating pathologic condition of the lung characterised by chronic inflammation, wall thickening and dilatation of the airways. Impaired mucociliary clearance renders the lungs susceptible to chronic infection which leads to chronic airway inflammation, progressive obstruction of the small airways and bronchial wall destruction [1].

To date, this vicious cycle of inflammation and infection is considered to arise from a number of causes either inherited or acquired. Thus, bronchiectasis is a final pathology emerging from a number of potential causes, which may require their own specific treatment.

The most common inherited cause of bronchiectasis in Caucasian populations is cystic fibrosis (CF); however, there is increasing recognition of significant numbers of subjects presenting with bronchiectasis from a variety of causes [2].

In non-CF bronchiectasis (NCFB), subjects show symptoms of chronic cough, increased sputum production, dyspnoea and malaise [3, 4], which may occur following infection or toxic insult due to immune deficiency or excessive immune response after e.g. allergic bronchopulmonary aspergillosis (ABPA). Evidence for the disease can be sought radiologically via computerised tomography (CT), scanning the lungs for thickening and dilatation of the bronchi in subjects for whom CF has been reasonably excluded with sweat testing and / or genetic analysis.

Reviews of NCFB reported a prevalence of bronchiectasis ranging from 4.2/100,000 for persons aged 18 to 34 years to 271.8/100,000 for those aged ≥75 years [5].

Further, prevalence was higher among women than men at all ages and also much higher in poor countries where it is a major cause of morbidity and mortality [6].

The airways of subjects with NCFB commonly become chronically infected with bacteria, the most common being *Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae* and *Pseudomonas aeruginosa (P. aeruginosa)*. *P. aeruginosa* is associated with worsening of symptoms and disease status.

A meta-analysis of 21 observational cohort studies with 3,683 NCFB patients [7] showed that chronic infection with *P. aeruginosa* was associated with a 6.6-fold increase in the rate of hospitalisation and a 3.0-fold increase in mortality compared with adult NCFB patients without chronic infection with *P. aeruginosa.*

However, there is no conclusive data in the literature on whether the presence of *P. aeruginosa* is correlated with accelerated decline of lung function [8] or not [9].

Treatment

Treatment approaches include a variety of pharmacotherapies, airway clearance and in selected cases surgery [3, 4].

Generally, therapy aims to either treat the underlying cause or the already established bronchiectasis.

Airway clearance techniques including postural drainage, active cycle breathing technique and chest wall percussion, have been used for many years to increase mucociliary clearance together with prevention of mucus retention and mucus plug formation. It allows a subject to expectorate sputum at a convenient time. However, evidence through controlled studies is limited to prove its objective usefulness in terms of disease modification or survival [3, 4].

Usage of mucolytics in NCFB is controversial. Human DNase does not appear to be as effective in NCFB as it is in CF and seems to be associated with an increase in NCFB

pulmonary exacerbation and hospitalisation rates and antibiotic use [10]. Other approaches enhancing airway clearance and sputum yield include the use of osmotic agents like nebulised hypertonic saline and inhalation of dry powder mannitol.

A wide range of antibiotic therapies is used in the management of bronchiectasis. They are either given as treatment for acute pulmonary exacerbations, generally administered orally, or as prophylactic long-term treatment (oral or nebulised) aiming to disrupt the vicious cycle of infection and inflammation. However, to penetrate scarred, thickened airway walls in bronchiectasis, normally high oral doses of antibiotics are required. To avoid such high doses, which potentially result in unacceptable side-effects, the nebulised route has been employed to achieve sufficient drug concentrations in the bronchial walls and their secretions.

Studies of inhaled antibiotics for the prevention of pulmonary exacerbations have yielded mixed results and none of these antibiotics is currently approved for this indication [11, 12, 13, 14, 15.].

Trial Rationale

To date, no therapies have been shown to cure or to reverse the progression of the disease.

In 2010, the British Thoracic Society published guidelines for the management of patients with NCFB [16]. The guidance recommends treating patients with NCFB, who are infected with *P. aeruginosa*, with chronic inhaled anti-pseudomonal antibiotics, namely gentamicin, tobramycin or colistimethate sodium.

More recently, the European Respiratory Society has published similar guidelines [17]. The European Respiratory Society guidelines were developed by an international multidisciplinary team of medical experts and NCFB patients. The first goal of the management of bronchiectasis specified by this group is the reduction of pulmonary exacerbations. Acute pulmonary exacerbations should be treated with 14 days of antibiotics. European Respiratory Society guidelines suggest long-term treatment with an inhaled antibiotic for adults with NCFB and chronic *P. aeruginosa* infection and the currently available evidence supports continuous use of nebulised colistin or gentamicin. There are no official guidelines for the treatment of NCFB patients in the US.

Colistimethate sodium is an antibacterial cationic cyclic polypeptide belonging to the polymyxin group; it is currently approved in Europe for both intravenous and inhaled administration and in the US for intravenous administration. In Europe, colistimethate sodium has been extensively used in clinical practice for over 30 years via the inhaled administration route, for the treatment of colonisation and infections of the lung by susceptible *P. aeruginosa* in patients with CF. The approved injectable forms of colistimethate sodium in the US are indicated for the treatment of acute or chronic infections due to sensitive strains of certain Gram-negative bacilli and are particularly indicated when the infection is caused by sensitive strains of *P. aeruginosa*.

Colistimethate sodium (1 million International Units [MIU], equivalent to 33 mg CBA) powder for nebuliser solution has been authorized and marketed in Europe by the Zambon SpA UK affiliate (Profile Pharma Ltd) since 2003 under the brand names Promixin® and Tadim® for nebulised treatment of colonisation and infections of the lung by susceptible *P. aeruginosa* in patients with CF. Authorisation was granted based on a bibliographic submission. The licensed dose in adults, adolescents, and children ≥ 2 years is 1-2 MIU (equivalent to 33-66 mg CBA) two to three times per day (max 6 MIU/198 mg CBA per day).

To date, 2 clinical studies with Promixin® (colistimethate sodium) have been completed and reported. One was a pharmacokinetic study in healthy subjects ( ), investigating the amount of colistimethate sodium absorbed across the lungs. This study found that the

administration of colistimethate sodium by inhalation in healthy subjects resulted in much lower systemic exposure than following i.v. administration. The absolute bioavailability was calculated to vary between 5% and 18% depending on the nebuliser. The administration of CMS by inhalation was well-tolerated and no safety concerns were identified. No Serious Adverse Events (SAEs) were reported.

The second ( ) was the predecessor to the current trial, investigating whether inhaled colistimethate sodium (Promixin®) increased the time to the next pulmonary exacerbation and improved the symptoms experienced by reducing the bacterial load in the lungs in subjects with NCFB infected with susceptible *P. aeruginosa* [13].

The trial enrolled bronchiectasis patients with two or more positive respiratory tract cultures for *P. aeruginosa* in the preceding 12 months and who were within three weeks of completing a course of antipseudomonal antibiotics for the treatment of an exacerbation. *P. aeruginosa* also had to be cultured from a sputum sample taken at the screening visit. Participants were randomised to receive colistimethate sodium (1 MIU [33 mg CBA]; n = 73) or placebo (0.45% saline; n = 71) via the CCI twice a day, for up to 6 months. The primary endpoint was time to exacerbation. Secondary endpoints included CCI

Median time (25% quartile) to exacerbation was 165 versus 111 days in the colistimethate sodium and placebo groups, respectively (p=0.11). Thirty-six of 73 patients (49%) in the colistimethate sodium group and 42 of 71 patients in the placebo group (59%) experienced a pulmonary exacerbation. Among the most adherent 75% of patients (adherence ≥81%), 27 of 54 (50%) of colistimethate sodium patients experienced an exacerbation compared to 39 of 54 (72%) in the adherent placebo group. The median time (25% quartile) to exacerbation was 168 days in the adherent colistimethate sodium group and 103 days in the adherent placebo group (p=0.028).

The colistimethate sodium group had CCI compared with placebo (in the intention-to-treat [ITT] population and in the adherent population).

There were no safety concerns. 14 SAEs have been reported in nine patients. The incidence of Adverse Events (AEs) leading to discontinuation was extremely low and similar between treatment groups. All AEs were mild to moderate in severity and no subject experienced significant bronchoconstriction whilst receiving study treatment. No Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported. There were no concerns with respect to renal toxicity or neuropathy. There was no evidence that the use of nebulized colistimethate led to the development of colistin-resistant isolates of *P. aeruginosa* or overgrowth of other bacteria.

On the basis of the outcome of the study and the scientific advice received from the British Medicines and Healthcare products Regulatory Agency (MHRA), two Phase 3 trials (PROMIS I and II) were designed as a 12 months double-blind, placebo-controlled treatment to investigate if nebulised colistimethate sodium increases the CCI in subjects with NCFB chronically infected with *P. aeruginosa*. The need to balance treatment groups for concomitant use of macrolides was also identified as a factor which could influence results and which has been controlled for in both studies by using an interactive web-based response system for treatment allocation.

However, the Sponsor subsequently received advice from the FDA requesting co-primary endpoints of CCI and number of CCI, extending the PROMIS II trial to 24-months placebo-controlled duration, as well as modifications to the study endpoints and other study aspects detailed in this amended protocol. This advice was following the FDA Advisory Committee reviews of 2 other

investigational treatments for NCFB, and what they considered to be more robust endpoints to assess efficacy.

As a consequence, this PROMIS I protocol was updated accordingly, however, still maintaining a 12-months placebo-controlled duration, per MHRA guidance and given that the second Phase 3 study investigated the 24 month duration period.

The change in primary endpoint resulted in an increase in study sample size and number of countries/sites; the Sponsor has extended the enrolment time and overall study duration accordingly. Following a Type C Meeting held with the FDA on 31st October 2018, it was agreed that a single primary endpoint of frequency of pulmonary exacerbations and 12-months placebo-controlled treatment duration would be acceptable as detailed in this amended protocol.

The safety profile of nebulised colistimethate sodium will also be evaluated over this period.

3.1. EVALUATION OF THE ANTICIPATED RISK/BENEFIT RATIO

Colistimethate sodium (commercially available as Promixin®/Tadim®) is indicated for the management of chronic pulmonary infections due to *P. aeruginosa* in adult and paediatric patients with CF.

Colistimethate sodium has a well-established safety profile in subjects with CF (Promixin® Summary of Product Characteristics [SmPC] [18]).

Patient exposure data for CF patients in key European markets using commercial colistimethate sodium drug product (Promixin®/Tadim®) delivered with the CCI nebulizer estimates the number of treatment days as 13,146,075 (March 2003 to 31st July 2017, inclusive), with a low level of spontaneous adverse drug reactions reported.

Common side-effects of nebulisation include coughing and bronchospasm with the first administration, observed in approximately 10% of subjects. Other common side effects on the respiratory system include chest tightness and bronchoconstriction.

During the trial, subjects will administer an inhaled short-acting bronchodilator (e.g. salbutamol/albuterol) provided by the Sponsor prior to each IMP administration in order to reduce the side-effects described above. If subjects prefer not to use the bronchodilator and tolerate IMP without it this is acceptable. To monitor subjects for bronchial hyperreactivity in response to inhaled colistimethate sodium which may develop with continued use, regular spirometric examinations are included in the trial schedule.

Further side-effects observed include hypersensitivity reactions such as skin rash and cases of sore throat or sore mouth (also potentially due to superinfection with *Candida* species).

High serum concentrations may lead to a reduction of pre-synaptic acetylcholine release and thus may prolong the effects of muscle relaxants and increase fatigue. In addition, high serum concentration may result in renal impairment; whilst this is highly unlikely during inhalation therapy, in the current protocol an evaluation of renal function will be performed at baseline and during treatment.

Colistimethate sodium should be used with extreme caution in subjects with porphyria.

It is anticipated that administration of colistimethate sodium, administered twice daily via the CCI for 12 months, may significantly reduce the frequency of pulmonary exacerbations compared to placebo in subjects with NCFB chronically infected with *P. aeruginosa*. Anticipated benefits to the subject randomised to colistimethate sodium include improved lung function and overall CCI

4. OBJECTIVES

The primary objective of the trial is to investigate the effect of the use of inhaled colistimethate sodium, administered twice daily via the CCI for 12 months, compared to placebo in subjects with NCFB chronically infected with *P. aeruginosa* on the frequency of pulmonary exacerbations.

The secondary objectives of the trial are to investigate the effect of the use of inhaled colistimethate sodium, administered twice daily via the CCI for 12 months, compared to placebo in subjects with NCFB chronically infected with *P. aeruginosa* on:

- CCI

All the trial variables are described in Section 18.2.

5. ETHICS REQUIREMENTS

This trial will be conducted in compliance with last version of Declaration of Helsinki; refer to the link https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ , with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), in particular E6(R2), with the applicable regulatory requirements and with Zambon and contract research organisation (CRO) standard operating procedures (SOPs).

6. DESIGN AND DURATION OF THE CLINICAL TRIAL

6.1. CLINICAL TRIAL 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 15 estimated countries.

Please refer to Appendix 1 for a trial flow chart.

The study will consist of a total of 7 clinic visits (see Section 8) with a follow-up phone call two weeks after discontinuation of treatment. Additional clinic visits, where feasible, and weekly phone calls will be conducted following pulmonary exacerbations (or any episodes

of pneumonia) until resolution, and a clinic visit may also be required during a pulmonary exacerbation or pneumonia (Section 8.8).

At Screening (Visit 1), subjects will be asked to provide Informed Consent prior to any trial related assessment and will be checked against inclusion and exclusion criteria. Their medical history will be recorded. Additionally, subjects will undergo 12-lead ECG, laboratory assessments and will provide sputum samples. These results will be available before Visit 2; if the Screening Visit sputum sample is negative for *P. aeruginosa*, up to two further samples may be collected and tested, within 30 days, after which, if all three are negative, the subject will be asked not to attend Visit 2 and will be deemed a Screen Failure (see Section 8.1).

However, should the Investigator deem it preferable to repeat screening, the subject can be re-screened once within 2 months after Visit 1. In this case the subject must re-consent to participate and all screening assessments must be performed again.

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

It is planned to enrol 210 subjects into each treatment group.

It is planned that subjects will attend for a further 5 visits at the sites at 1, 3, 6, 9, and 12 months after Randomization (visit 2) (i.e. Visits 3, 4, 5, 6, and 7) and will have 1 follow-up phone call at 12.5 months.

Procedures performed at all clinical visits are detailed in Section 8.0 and will include documentation of concomitant medications and treatment emergent adverse events (TEAEs) as well as spirometry to determine forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Additionally, the subjects will be asked by the Investigator for information on any NCFB pulmonary exacerbations that were not reported.

Further sputum samples will be collected at Visits 2, 3, 5 and 7, to be analysed CCI [redacted]. Sputum samples collected at Screening (Visit 1) and at the end of treatment (Visit 7) will have isolates retained by the central laboratory for later analysis CCI [redacted]

At Visits 2, and at each post-baseline study visit, [redacted] will be assessed using the CCI [redacted].

In case subjects feel that they are experiencing a NCFB pulmonary exacerbation (as defined in Section 18.2), they should contact the investigational site immediately to discuss their symptoms and, if feasible, to arrange an Exacerbation Visit (which should take place within 2 working days of the exacerbation starting, if possible). The Investigator will check whether the pulmonary exacerbation meets the criteria defined in this Clinical Trial Protocol (CTP), will decide on an appropriate course of action (including systemic antibiotic treatment, if required) and will perform the assessments defined in the Section 8.8.

6.2. DURATION OF CLINICAL TRIAL

The overall study duration (from first patient first visit to last patient last visit) is expected to be from Q2 2017 to Q4 2020.

The maximum expected duration of participation in this trial for an individual subject, from Visit 1 (Screening) to the follow-up phone call is 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 had the follow-up phone call. The end of the trial for the purposes of the primary statistical analysis is defined as the last subject completing the trial.

If the trial is prematurely stopped, please refer to Section 15.

7. CLINICAL TRIAL POPULATION

7.1. NUMBER OF SUBJECTS

A total of 420 subjects (210 in each treatment group) are planned to be enrolled into the trial. The enrolment is competitive among sites.

For a description of sample size calculation, please refer to Section 18.3.

7.2. SELECTION OF SUBJECTS

7.2.1. INCLUSION CRITERIA

Subjects can be included in the trial if they meet all the inclusion criteria listed below:

1) are able and willing to give informed consent, following a detailed explanation of participation in the protocol and signed consent obtained;
2) are aged 18 years or older of either gender;
3) are diagnosed with NCFB by computerised tomography (CT) or high resolution CT (HRCT) as recorded in the subject's notes and this is their predominant condition being treated;
4) had at least 2 NCFB pulmonary exacerbations requiring oral or inhaled antibiotics or 1 NCFB pulmonary exacerbation requiring intravenous antibiotics in the 12 months preceding the Screening Visit (Visit 1) and had no NCFB pulmonary exacerbation with or without treatment during the period between Visit 1 and Visit 2;
5) have a documented history of *P. aeruginosa* infection;
6) are clinically stable and have not required a change in pulmonary treatment for at least 30 days before the Screening Visit (Visit 1);
7) have pre-bronchodilator FEV_1 ≥25% of predicted;
8) had a positive sputum culture for *P. aeruginosa* from an adequate sample taken at the Screening Visit (Visit 1) or during the screening period.

7.2.2. EXCLUSION CRITERIA

Subjects are not eligible for the trial if they meet one or more of the exclusion criteria listed below:

1) known bronchiectasis as a consequence of cystic fibrosis (CF);
2) known history of hypogammaglobulinaemia requiring treatment with immunoglobulin, unless fully replaced and considered immuno-competent by the Investigator;
3) myasthenia gravis or porphyria;
4) severe cardiovascular disease such as severe uncontrolled hypertension, ischaemic heart disease or cardiac arrhythmia and any other conditions that would confound the evaluation of safety, in the opinion of the Investigator;

5) had major surgery in the 3 months prior to the Screening Visit (Visit 1) or planned inpatient major surgery during the study period;
6) receiving treatment for allergic bronchopulmonary aspergillosis (ABPA);
7) had massive haemoptysis (greater than or equal to 300 mL or requiring blood transfusion) in the preceding 4 weeks before the Screening Visit (Visit 1) or between Visit 1 and Visit 2;
8) respiratory failure that would compromise patient safety or confound the evaluation of safety or efficacy of the study in the opinion of the Investigator;
9) current active malignancy, except for basal cell carcinoma or squamous cell carcinoma of the skin without metastases;
10) taking immunosuppressive medications (such as azathioprine, cyclosporine, tacrolimus, sirolimus, mycophenolate, rituximab), and/or anti-cytokine medications (such as anti-IL-6 and anti-tumour alpha necrosis factor products) in the preceding year before the Screening Visit (Visit 1);
11) known history of human immunodeficiency virus (HIV);
12) current treatment for non-tuberculous mycobacterium (NTM) lung disease or tuberculosis.
13) known or suspected to be allergic or unable to tolerate colistimethate sodium (intravenous or inhaled) or other polymixins, including previous evidence of bronchial hyper-reactivity following inhaled colistimethate sodium;
14) treatment with long term (≥ 30 days) prednisone at a dose greater than 15 mg a day (or equivalent dose of any other corticosteroid) within six months of the Screening Visit (Visit 1);
15) new maintenance treatment with any oral macrolides (e.g. azithromycin/erythromycin/clarithromycin) started within 30 days of the Screening Visit (Visit 1) and between Visit 1 and Visit 2;
16) use of any intravenous or intramuscular or oral or inhaled anti-pseudomonal antibiotic (except chronic oral macrolide treatment with a stable dose) within 30 days prior to the Screening Visit (Visit 1) and between Visit 1 and Visit 2;
17) pregnant or breast feeding or plan to become pregnant over the next year or of child-bearing potential and unwilling to use a reliable method of contraception for at least one month before randomisation and throughout their involvement in the trial;
18) significant abnormality in clinical evaluations and/or laboratory tests (physical examination, vital signs, haematology, clinical chemistry, clinically relevant impaired renal function, defined as serum creatinine levels ≥2.0x upper limit of normal, ECG) endangering the safe participation of the patient in the study at the Screening Visit (Visit 1) and during the study;
19) participated in another investigational, interventional trial within 30 days prior to the Screening Visit (Visit 1);
20) in the opinion of the Investigator not suitable for inclusion for whatever reason.

Contraceptive methods

Safety in human pregnancy has not been established. Animal studies do not indicate a teratogenic potential. However, there is evidence that colistimethate sodium crosses the placenta and, consequently, there is potential for foetal toxicity if administered during pregnancy. Colistimethate sodium should only be given during pregnancy if the benefits outweigh any potential risk.

Female subjects can be enrolled if they are either post-menopausal for at least 2 years, or surgically sterilized or have undergone hysterectomy.

Female subjects of child-bearing potential must be willing to avoid pregnancy. They are required to have a negative pregnancy test at inclusion (see Section 9.1.4), and should use highly effective methods of birth control for 1 month prior to randomisation, throughout the trial duration and up to 1 month after the last dose of IMP, which include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- surgical sterilization (e.g. bilateral tubal ligation or occlusion)
- male sterilization (vasectomised partner)
- sexual abstinence.

Throughout the course of the study male participants with female partners of child-bearing potential must abstain from sexual intercourse, use condoms or use effective contraceptive precautions. Male participants must also not take part in the donation of sperm whilst enrolled on the study.

8. OVERALL CLINICAL TRIAL SCHEDULE

The current trial will include 7 planned clinical visits at the investigational site and 1 follow-up telephone call. A detailed flow chart showing the procedures performed is given in Appendix 1. The following sections outline the procedures to be performed at the individual visits.

8.1. VISIT 1 - SCREENING VISIT (WITHIN 30 DAYS OF VISIT 2)

At Visit 1 (Screening), the following procedures will be performed:

- obtain written Informed Consent;
- documentation of medical history and subject demographic data;
- documentation of previous and concomitant medications (including long term antibiotic use for NCFB pulmonary infection prophylaxis, and in particular oral azithromycin/erythromycin/clarithromycin administration in the last 12 months, and any prior use of nebulised colistin or colistimethate sodium or other inhaled/oral antibiotic);
- check number of NCFB pulmonary exacerbations in the preceding year;
- check of inclusion/exclusion criteria;
- assessment of vital signs (Section 9.1.3);
- physical examination (including chest auscultation);
- 12-lead ECG in the supine position after 5 minutes of rest (evaluation by local medical staff) in order to verify the subject's eligibility (Section 9.1.6);
- blood samples for clinical laboratory assessments (haematology, clinical chemistry and renal function tests). (Section 9.1.4);
- dip-stick pregnancy test for women of child-bearing potential.
- spirometry (if not done in the 30 days beforehand); pre-bronchodilator FEV_1 must be ≥30% of predicted for the patient normal value (determined using Global Lung Function Initiative [GLI] reference equations);

- collection of CCI [redacted] (results have to be available by Visit 2; if negative, the subject will be asked to return to the clinic for a repeat sputum sample prior to Visit 2 - if this second sample is also negative, one further sample may be collected for analysis; thereafter, the subject will be a screen failure and will not be required to attend Visit 2);
- instruction of subjects on actions to be taken in case of NCFB pulmonary exacerbations.

The Investigator will arrange an appointment for Visit 2 within 30 days.

8.2. VISIT 2 - RANDOMISATION VISIT (DAY 0)

At Visit 2 (Randomisation), the following procedures will be performed:

- check if subject is still eligible according to inclusion and exclusion criteria and check of screen failure criteria for Visit 2;
- documentation of concomitant medications (including azithromycin/erythromycin/ clarithromycin use) or treatments;
- record details of any AEs since the Screening Visit (Visit 1);
- training and completion of CCI [redacted] on electronic clinical outcome assessment (eCOA) device before other study procedures;
- dip-stick pregnancy test for women of child-bearing potential.
- collection of CCI [redacted];
- randomisation by Interactive Web Response System (IWRS) and treatment kits assignment;
- dispensing of, and subject training on, CCI [redacted] device including the use of the [redacted] disc;
- subject training on IMP preparation, inhaled bronchodilator use and subject's card dispensing;
- first IMP administration under clinical supervision (at least 10 minutes after inhalation of short-acting bronchodilator; if the patient prefers not to use a bronchodilator this should be documented and the lack of bronchial hyper-reactivity after IMP administration documented);
- spirometry, including assessment of FEV_1 and FVC pre-bronchodilator and 30 ± 10 minutes post-IMP dose (**Note:** in case of a >15% decrease - not due to poor technique - in FEV_1 from pre-bronchodilator baseline after first IMP intake, or clinically determined bronchospasm, the subject will be immediately withdrawn from the trial);
- dispensing of sufficient IMP kits and inhaled bronchodilator for the treatment period until Visit 3;
- instruction of subjects on actions to be taken in case of CCI [redacted].

The Investigator will arrange an appointment for Visit 3 (28 days ± 1week).

In addition, the Investigator will call the subject after 1 week to ensure that there are no problems with the mixing of IMP, the use of the nebuliser device and will also ask about any AEs, including any CCI [redacted] due to CCI [redacted], and any medical device malfunctions and/or incidents (see Section 16.3.2).

8.3. VISIT 3 (DAY 28 ± 1 WEEK)

At Visit 3, the following procedures will be performed:

- documentation of concomitant medications (including azithromycin/erythromycin/ clarithromycin use) or treatments;
- check for occurrence of CCI not reported by the subject (Note: whether an unreported CCI occurred will be assessed retrospectively by the Investigator by asking about the prescription of antibiotics by other physicians; if yes, the CCI and its duration will be recorded in the electronic Case Report Forms [eCRF]);
- record details of any AEs since previous visit;
- record details of any medical device malfunction and/or incidents since previous visit (Section 16.3.2);
- record of CCI and days of CCI due to CCI ;
- completion of CCI on the eCOA device before other study procedures;
- dip-stick pregnancy test for women of child-bearing potential;
- blood samples for renal function tests (Section 9.1.4);
- collection of CCI
- spirometry, including assessment of FEV_1 and FVC;
- review of CCI data using the data analyser provided to sites for the ongoing assessment of adherence (and re-training of subjects, if appropriate);
- IMP collection and accountability (used/unused vials), including check of bronchodilator use and dispensing of sufficient IMP kits and inhaled bronchodilator for the treatment period until Visit 4;
- instruction of subjects on actions to be taken in case of NCFB pulmonary exacerbations.

The Investigator will arrange an appointment for Visit 4 (within 2 months ± 1week).

8.4. VISIT 4 (3 MONTHS ± 1 WEEK) TO VISIT 6 (9 MONTHS ± 1 WEEK), INCLUSIVE

At Visit 4 to Visit 6, inclusive, the following procedures will be performed:

- documentation of concomitant medications (including azithromycin/erythromycin/ clarithromycin use) or treatments;
- check for occurrence of CCI not reported by the subject (Note: whether an unreported CCI occurred will be assessed retrospectively by the Investigator by asking about the prescription of antibiotics by other physicians; if yes, the CCI and its duration will be recorded in the eCRF);
- record details of any AEs since previous visit;
- record details of any medical device malfunctions and/or incidents since previous visit (Section 16.3.2);
- record of CCI and days of CCI due to CCI since the previous visit;
- blood samples for clinical laboratory assessments (haematology, clinical chemistry and renal function tests) at Visit 5 only (Section 9.1.4);
- completion of CCI on eCOA device before study procedures;
- dip-stick pregnancy test for women of child-bearing potential;

- collection of [redacted];
- spirometry, including assessment of FEV_1 and FVC;
- review of [redacted] data using the data analyser provided to sites for the ongoing assessment of adherence (and re-training of subjects, if appropriate);
- IMP collection and accountability (used/unused vials), including check of bronchodilator use and dispensing of sufficient IMP kits and inhaled bronchodilator for the treatment period until the subsequent visit;
- instruction of subjects on actions to be taken in case of NCFB pulmonary exacerbations.

The Investigator will arrange an appointment for the subsequent visit.

8.5. VISIT 7 (12 MONTHS ± 1 WEEK); END OF TREATMENT

At Visit 7, the following procedures will be performed:

- documentation of concomitant medications (including azithromycin/erythromycin/ clarithromycin use) or treatments;
- check of occurrence of [redacted] not reported by the subject (Note: whether an unreported [redacted] occurred will be assessed retrospectively by the Investigator by asking about the prescription of antibiotics by other physicians; if yes, the [redacted] and its duration will be recorded in the eCRF);
- record details of any AEs since previous visit;
- record details of any medical device malfunctions and/or incidents since previous visit (See section 16.3.2);
- record of [redacted] and days of [redacted] due to [redacted] since previous visit;
- completion of [redacted] on eCOA device before any study procedures;
- assessment of vital signs (Section 9.1.3);
- physical examination (including chest auscultation);
- 12-lead ECG in the supine position after 5 minutes of rest (with evaluation by local medical staff, Section 9.1.6);
- dip-stick pregnancy test for women of child-bearing potential;
- blood samples for clinical laboratory assessments (haematology, clinical chemistry and renal function tests, Section 9.1.4);
- collection of [redacted];
- last IMP administration under clinical supervision (at least 10 minutes after inhalation of short-acting bronchodilator);
- spirometry, including assessment of FEV_1 and FVC pre-bronchodilator and 30 ± 10 minutes post-IMP dose;
- collection of [redacted] device and disc (to be transferred to [redacted] for download);
- IMP collection and accountability (used/unused vials) and collection of bronchodilator.

8.6. FOLLOW-UP PHONE CALL (2 WEEKS ± 3 DAYS AFTER END OF TREATMENT)

A follow-up phone call will be performed at 2 weeks ± 3 days after the discontinuation of IMP.

The following procedures will be performed during the call:

- documentation of concomitant medications;
- AE monitoring.

If the result of the susceptibility test at the end of treatment (Visit 7) suggests the subject is resistant to colistin, he/she will be called for an extra visit with sputum collection for analysis of CCI .

8.7. EXACERBATION VISIT/CONTACT

Subjects will be trained by the Investigator to recognise signs and symptoms of NCFB pulmonary exacerbations.

At each post-randomisation visit the patient will be reminded about how to recognise symptoms of a NCFB pulmonary exacerbation and instructed to contact the site as soon as they have experienced these symptoms for 24 hours. If feasible, the subject will be asked to attend the clinic at their earliest convenience. If it is not practical for the subject to make an additional clinic visit then relevant information will be collected via phone and the subject will be asked to send a sputum sample to the clinic.

Any episodes of pneumonia during the trial should be considered as severe pulmonary exacerbations and will also require a clinic visit, if feasible.

The Investigator will decide if symptoms represent a NCFB pulmonary exacerbation meeting the protocol-defined criteria or not and on the appropriate course of action.

It will be clinically determined if the subject requires systemic antibiotic therapy (oral or intravenous) in addition to IMP administration or whether IMP administration should be temporarily interrupted (see below). Treatment of a NCFB pulmonary exacerbation will follow current treatment regimens used in the respective participating trial site.

If subjects need to be admitted to hospital for intravenous antibiotics, they should be visited by the research staff for an assessment within 72 hours of admission (where possible). If the subject is admitted to a hospital that is not the investigational site, the assessments should be carried out (where possible) by the admitting hospital under the direction of the investigational site. These assessments will include those collected during exacerbation visits/contacts and will include details regarding any interruption of IMP administration. In these circumstances, every effort should be made to complete all assessments although it is recognised that this might not be possible.

Telephone calls will be made to patients on a weekly basis during a NCFB pulmonary exacerbation until resolution to assess the progression of symptoms to and to determine whether systemic antibiotic treatment is ongoing. A telephone script will be provided to sites and responses to standardised questions will be collected in relevant eCRFs.

Resolution of a NCFB pulmonary exacerbation is defined as the date of completion of the required course of systemic antibiotic treatment or the Investigator's judgement that the NCFB pulmonary exacerbation has resolved, whichever is later. Exacerbations occurring less than 14 days after the end of a course of systemic antibiotics for a NCFB pulmonary exacerbation will be considered as a single event (see Section 9.1.5).

IMP administration may be temporarily interrupted during the time of systemic antibiotic treatment due to a pulmonary exacerbation based on the Investigator's judgement; thereafter, the study treatment should restart as soon as possible. Stop date and re-start

date will be recorded in the relevant eCRF. The occurrence of a pulmonary exacerbation does not mandate the discontinuation of the subject from the trial, unless it occurs between Visit 1 and Visit 2 and /or the Investigator believes discontinuation is in the subject's best interest.

The following assessment will be performed at an Exacerbation Visit or Phone contact, and all details of the pulmonary exacerbation have to be recorded:

- start date and duration of all symptoms since the start;
- all symptoms present which support the NCFB pulmonary exacerbation diagnosis;
- all concomitant medications, especially systemic antibiotics;
- physical examinations and vital signs (if attending the clinic);
- date of CCI [redacted] and/or days of CCI [redacted] (if any);
- measurement and recording of FEV_1 and FVC (if feasible);
- pulmonary exacerbation as AE/SAE according to protocol and followed until resolution, including weekly follow-up phone calls as detailed above;
- collection of CCI [redacted] for other antibacterial panels. If subjects are unable to attend the clinic then suitable arrangements will be made to obtain an additional CCI [redacted], if feasible.

9. METHODOLOGY

9.1. METHODS OF ASSESSMENT

9.1.1. DEMOGRAPHY AND MEDICAL HISTORY

At Visit 1 (Screening) the subjects' demographic data will be documented, (including age, ethnicity, gender, height, weight as well as smoking history and alcohol use), date of diagnosis of NCFB and if known, the underlying cause of the bronchiectasis. Body weight will also be measured at Visit 7.

Further, the subjects' medical history will be documented, i.e. relevant past and/or currently ongoing conditions. This includes details regarding pulmonary exacerbations in the last 12 months and the collection of a report on CT/HRCT results, to confirm the diagnosis of NCFB as per inclusion criterion 3 (see Section 7.2.1).

Any relevant worsening in ongoing conditions during the trial (i.e. since Visit 1) are required to be recorded as AEs in the eCRF (see Section 16).

9.1.2. PHYSICAL EXAMINATION

At Visit 1 and Visit 7, a physical examination of general body systems will be performed according to current medical standard and site practice. The examination has to include a chest auscultation. Any relevant worsening regarding physical examination results of a subject since Visit 1 should be recorded as AEs in the eCRF (see Section 16).

9.1.3. VITAL SIGNS

At Visit 1 and Visit 7, vital signs will be recorded according to site practice and before spirometry testing. This will include heart rate, systolic/diastolic blood pressure (measured after at least 5 minutes in the supine position), respiratory rate, and body temperature.

Automatic or manual devices may be used, but the same device should be used for any given subject throughout the trial. The same arm should be used for all measurements.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as “normal”, “abnormal clinically significant” or “abnormal not clinically significant”. Abnormalities of clinical significance will be reported as AEs.

Any clinically relevant worsening of vital signs of a subject since Visit 1 should be recorded as AEs in the eCRF (see Section 16).

9.1.4. LABORATORY EVALUATIONS

Routine laboratory evaluations will be performed at the Screening Visit (Visit 1), Visit 5 and Visit 7. The haematology and clinical chemistry parameters detailed in Table 1 will be analyzed at the central laboratory using standard, validated laboratory methods.

Renal function will be monitored by laboratory tests (creatinine, Blood Urea Nitrogen [BUN]) performed at the Screening Visit (Visit 1) and during the treatment: at Day 28 of treatment (Visit 3), after 6 months (Visit 5) and at the end of treatment (Visit 7).

Subjects with clinically relevant impaired renal function (as defined by serum creatinine levels ≥2.0x upper limit of normal) will be discontinued.

Note that at Visit 1 and Visit 7 the blood samples for these assessments must be collected after the 12-lead ECG assessments have been performed.

A dipstick urine pregnancy test for women of child-bearing potential will be performed at the investigational site at the Screening Visit (Visit 1) and at all scheduled study visits thereafter.

Female subjects who become pregnant during the trial must be withdrawn from the trial without delay and will be followed up to determine the outcome of the pregnancy. The Investigator is required to inform the Sponsor of a subject’s pregnancy and the estimated date of delivery. Reporting requirements are outlined in Section 16.10.

Clinical laboratory tests will be reviewed for results of potential clinical significance before Visit 2 to confirm patient’s eligibility and during the trial, as appropriate. Clinically significant laboratory abnormalities arising from Visit 2 onwards are considered to be AEs. Where possible, a diagnosis should be ascribed to the abnormal lab test.

If the Investigator determines a laboratory abnormality to be clinically significant, it constitutes an AE, excluding abnormalities detected at Screening Visit (Visit 1).

Table 1 CLINICAL LABORATORY EVALUATIONS			
Hematology: at the Screening Visit (Visit 1), Visit 5 and Visit 7			
Hematocrit	Hemoglobin	Platelet count	Red blood cell count
White blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils)			
Clinical Chemistry at the Screening Visit (Visit 1), Visit 5 and Visit 7			
BUN*	Chloride	AST	
Creatinine*	Uric acid	ALT	
Sodium	Amylase	GGT	
Potassium	ALP	Bilirubin (direct and total)	
Calcium			
Pregnancy Test:			
Urine β-hCG (dipstick) at the Screening Visit (Visit 1) and at all visits thereafter			

* These evaluations will also be performed at Visit 3

9.1.5. EFFICACY EVALUATIONS

Pulmonary Exacerbations

The primary efficacy assessment for an individual subject is the frequency of pulmonary exacerbations.

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.

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 judgment that the NCFB pulmonary exacerbation has resolved, 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. If the subject is not better at the end of an initial 14-day course of systemic antibiotics, then the antibiotic should be continued for an additional standard treatment period (or escalated to intravenous therapy) in accordance with standard clinical practice.

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

Procedures to be followed in case a subject experiences symptoms suggestive of a pulmonary exacerbation are described in Section 8.8 (Exacerbation Visit/Contact).

CCI

In this trial, CCI

The CCI is a validated 50-item symptom questionnaire developed to measure health status and QoL in subjects with obstructive airway diseases [19, 20].

CCI . Scores will be collected for these 3 domains and the Total score will be produced.

The CCI is a validated self-administered, patient reported outcome measure assessing CCI for subjects with NCFB [21, 22].

CCI and was developed for use in clinical trials and routine clinical practice.

The questionnaires will be completed by the subjects at Visit 2 (Randomisation), and at each subsequent study visit prior to any study procedures using an eCOA device, i.e. SITEpro Tablet. The device will be provided by CCI . and is an electronic data collection system used to collect data at sites.

During Visit 2, appropriate training will be provided to the subjects on how to correctly complete the questionnaires on the device.

To utilise the device, the Investigator has to enter the screening number. Then the device will present the questionnaires for completion by the subject. To ensure that all visits are completed as defined in this CTP, the Investigator will select the appropriate visit number from the options on the screen before handing the device to the subject.

After completing the assessments as instructed, the subject will return the device to the Investigator who will then complete a data transfer to record the subject data in the trial database. To ensure that sites are not compromised with respect to the study blinding, the Investigator will not be able to view the responses provided by the subject.

The data transfer will be performed every time a subject completes the questionnaires on the eCOA device.

CCI

For the purposes of subject eligibility only, two discrete CCI (of 2.5 mL each) may be collected with the first sample being sent to the local laboratory and the second sample sent refrigerated to CCI or CCI on the day of collection. These may be collected by the patient at home in the morning of the visit and brought to clinic. After collection, the samples should be kept refrigerated (2ºC to 8ºC) as much as possible.

This is only permitted if the local laboratory is able to analyse CCI . The Institution must provide copies of the relevant laboratory accreditations (ISO 15189 Medical Laboratories, ISO/IEC 17025, or equivalent) prior to local positive results being considered acceptable for enrolment. If results are disparate (and the local result is positive but the central result negative) sites need to contact the Sponsor for confirmation that the subject can be enrolled.

Subsequently, CCI will be collected at each visit with the exception of Visits 4 and 6 as well as at any Exacerbation Visit (including episodes of pneumonia). Two samples may be taken during the clinic visit or at home on the morning of the visit, with the CCI only being sent for analysis. They will be sent refrigerated on the day of collection for analysis to CCI, specialized in microbiological analyses. CCI will be responsible for all aspects of the CCI analyses, including preparation of laboratory kits to be provided to investigational sites and will perform laboratory data management activities.

For analysis of CCI these CCI will be collected in sterile transport tubes and shipped refrigerated to the microbiological laboratory by selected courier to preferably arrive at the laboratory within 48 hours after collection.

Results of this quantitative analysis for CCI will be presented as colony forming units (CFU) count per gram. Additionally, results from Visit 1 (Screening) and Visit 7 (End of Treatment) will be made available to the Investigator in the form of laboratory reports via fax/email for the subjects' following visit/contact and transferred to the trial database according to pre-defined criteria. Results from other visits will not be reported directly to the Investigator in order not to bias safety and efficacy evaluations. The CCI will also be evaluated at specific visits from the samples (see Section 9.1.6).

More details on laboratory analyses and logistics can be found in the laboratory manual.

CCI Download

The subjects will administer the IMP via the CCI device twice daily which is activated by a disc provided with the CCI. Subjects will receive appropriate training on the use of the CCI device (including written instructions) and on preparation of the IMP to be used in the CCI. Subjects will perform the first administration of IMP under supervision of the site personnel during Visit 2 and they will be informed that the device will log their IMP usage. When subjects self-administer the IMP via the CCI device, the time of day, length of nebulisation and amount of IMP administered are stored in the device.

During the trial, adherence will be assessed on-site by the Investigator on an ongoing basis by downloading the data from the CCI into a data analyser installed in laptops provided by the Sponsor. In addition, drug accountability, assessing the amount of IMP used and not used by a subject (see Section 11.4) will be performed. The data remains on the CCI so it can be fully analysed at the end of the study.

After the end of treatment, i.e. Visit 7, the device use data from the CCI will be downloaded to the laptop using instructions provided to the site personnel. The data can then be sent electronically to the CRO or CCI as per instructions. Alternatively, the device can be stored and returned to CCI with returned IMP. CCI will then send the device on to CCI (the CCI manufacturer) who will download the data and send it on to the CRO. As the CCI system records all information on the doses of IMP taken, these data will be used to determine overall adherence.

9.1.6. SAFETY EVALUATIONS

Adverse Events

AEs will be recorded by the Investigator in the appropriate eCRF Section starting with the date of informed consent until the follow-up phone call. At each contact (i.e. clinical visit or phone call), subjects will be asked in a non-leading manner if they experienced any AEs.

All AEs occurring from the day of the first IMP administration, i.e. Visit 2, until the end of the trial, i.e. follow-up phone call, will be considered as TEAEs.

(Note: A pulmonary exacerbation will be reported as an AE or serious AE [SAE]; pulmonary exacerbations will also be captured as efficacy assessments).

For definitions and reporting of AEs and SAEs, see Section 16.

Lung Function by Means of Spirometry

Spirometry measurements of FEV_1 and FVC (predicted values will be as per GLI reference equations [23]) will be performed at Visit 1 (if not performed in the preceding 30 days) to verify the eligibility of the subject (see inclusion criteria in Section 7.2.1), and at Visit 2 through Visit 7.

Lung function measurement and daily calibration of the spirometer will be performed according to the standardised methods described by the American Thoracic Society/European Respiratory Society. It is suggested that, in each centre, the model of the spirometer used does not change during the study.

Lung function measurements will be done at approximately the same time of the day during clinic visits (dependent on IMP administration) with subjects either standing or sitting (for each subject, this should be consistent throughout the trial) with the nose clipped after at least 10 minutes rest. Calibration of the spirometer must be performed preferably by the same Investigator at each visit prior to spirometry measurements and the reports must be kept with the source trial documents.

For FEV_1 and FVC the highest value from 3 technically satisfactory attempts will be considered (irrespective of the curve they come from).

At Visit 2 and Visit 7, FEV_1 and FVC will be measured and recorded prior to the inhaled short-acting bronchodilator (e.g. salbutamol/albuterol) administration (pre-dose) and 30 ± 10 minutes post-IMP. Note: the IMP will always be administered 10-15 minutes after bronchodilator. In case a subject's FEV_1 decreases by >15% - not due to poor technique - at the post-dose reading and/or in the case of clinically determined bronchospasm, the subject will be withdrawn from the trial (see exclusion criteria in Section 7.2.2).

At all other visits, FEV_1 and FVC will be measured as above.

CCI and Other Species

Besides CCI analysis (see Section 9.1.5), CCI will be evaluated from CCI collected at each visit. The CCI testing will be done using a minimal inhibitory concentration (MIC) method. Testing of CCI with other antibacterial panels will also be conducted for samples collected during pulmonary exacerbations.

If CCI is detected and/or any isolate shows a significant rise in MIC (i.e. showing greater than a four-fold change in colistimethate sodium MIC) genotyping studies on CCI isolates may be conducted to determine if the change in MIC was due to microbiological recurrence or re-infection.

CCI collected at Screening (Visit 1) and at the end of treatment (Visit 7) will have isolates retained by the central laboratory for later analysis for CCI as well as the emergence of CCI and any developing resistance.

More details on laboratory analyses and logistics can be found in the laboratory manual.

12-lead Electrocardiogram

Computerized 12-lead ECG recordings will be obtained at each study centre using site machines at the Screening Visit (Visit 1) to verify the eligibility of the subject, and at Visit 7/End of Treatment.

ECGs will be performed after obtaining vital signs. Prior to recording, the subject should be at rest for at least 5 mins.

ECGs will be evaluated by the Investigator/local medical staff and the recording will be reported in the eCRF as “normal”, “abnormal clinically significant” or “abnormal not clinically significant”.

If abnormalities of clinical significance are recorded at Visit 1, the subject will be excluded from the trial (see exclusion criteria in Section 7.2.2); abnormalities of clinical significance recorded at Visit 7 will be reported as AEs.

Repeat measurements will be performed if needed.

9.2. ADHERENCE WITH IMP DOSING REGIMEN

The Investigator will assess the subjects’ adherence with the IMP dosing regimen on an ongoing basis by the data downloaded from the CCI device into a data analyser installed in laptops provided by the Sponsor.

Information on data download from the CCI logging system is given in Section 9.1.5.

The Investigator will also assess the amount of IMP dispensed, used (i.e. returned open vials) and not used (i.e. returned, unopened vials) at all clinical visits, starting with Visit 2 (first dose) up to the day of the last dose (Visit 7/End of Treatment).

IMP inventory and accountability records will be maintained within IWRS.

In the event that adherence is less than approximately 80% at any visit, adherence will be discussed with the subject and appropriate re-training will be given by site staff.

9.3. PHARMACODYNAMICS

Not applicable.

9.4. PHARMACOKINETICS

Not applicable.

10. PRIOR AND CONCOMITANT TREATMENTS

At Visit 1 (Screening), all prior and concomitant medications, including antibiotics, and over-the-counter products used by an individual subject within 1 month prior to the Screening Visit (Visit 1) will be documented in the eCRF.

In particular, any prior use of inhaled colistimethate sodium or colistin or other inhaled antibiotic, if stopped within 1 month prior to Visit 1, must be documented.

The following will be recorded:

- Dates of administration including start and end dates;
- Dosage information including dose and frequency;
- Reason for use.

During all subsequent clinical visits, the Investigator will document any changes in concomitant medications or use of rescue medication.

The following chronic treatments are permitted during the trial:

- oral macrolides (e.g. azithromycin/erythromycin/clarithromycin); Note: the decision whether concomitant antibiotic therapy should be administered to a subject will have been taken at least 30 days prior to Screening [Visit 1]; it is recommended to maintain a stable dose and continue the treatment throughout the trial;
- inhaled long-acting bronchodilators;
- inhaled short or long-acting muscarinic antagonists;
- inhaled corticosteroids;
- oral prednisone at a stable dose less than or equal to 15 mg a day or equivalent dose of any oral corticosteroid;
- methylxanthines at stable unchanged doses;
- leukotriene receptor antagonists;
- roflumilast;
- mucoactive treatments (nebulised hypertonic saline, nebulised isotonic saline, dry powder mannitol, nebulised dornase alpha, nebulised N-acetylcysteine) and oral mucolytics or expectorants, provided they had been a regular medication for at least 30 days.

The following medications may be used concomitantly with caution:

- non-depolarising muscle relaxants;
- other nephrotoxic or neurotoxic medications (e.g. cephalothin sodium, aminoglycosides, non-depolarising muscle relaxants) including those administered intravenously or intramuscularly;

For non-permitted medications, please see Exclusion Criteria (Section 7.2.2).

10.1. RESCUE MEDICATION

Rescue medication for NCFB pulmonary exacerbations allowed in the study include:

- acute and/or short-term administration of oral/intravenous bronchodilators and corticosteroids, if required;
- systemic (oral or intravenous) antibiotics according to current treatment regimens used at the participating sites;
- acute and/or short-term administration of oxygen therapy/ventilator assistance.

At each visit subjects will be asked about any rescue medications they have taken to self-treat at home.

Rescue medication prescribed by the Investigator for a pulmonary exacerbation will be documented.

The following will be recorded:

- Dates of administration including start and end dates;
- Dosage information including dose and frequency;
- Reason for use.

11. INVESTIGATIONAL MEDICINAL PRODUCT

11.1. INVESTIGATIONAL MEDICINAL PRODUCT SUPPLIES AND PACKAGING

Colistimethate sodium and placebo will be supplied in 30-vial packs with the CCI device containing a disc to activate the aerosol device.

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). The product is manufactured by CCI .

Identical sterile vials for placebo will be manufactured by CCI . 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.

The vehicle will be 0.45% sodium chloride sterile solution provided in plastic ampoules sealed in aluminium pouches containing a deliverable 1.0 mL of 0.45% NaCl manufactured by CCI .

No special precautions for storage are required for the IMP.

All IMP, vehicles, inhaled short-acting bronchodilator (e.g. salbutamol/albuterol), and CCI devices will be shipped to sites by CCI where CCI is in charge of masking vials, packaging and labelling.

IMPs will be labelled according to Good Manufacturing Practice (GMP) and country specific regulations as required by the regulatory agencies in the countries where the trial is conducted. Labels will be printed in a booklet with all local languages or as a single panel label. Allocation of IMP will be managed through the IWRS used for the trial.

The CCI system will be provided as the commercially available devices.

The inhaled short-acting bronchodilator (e.g. salbutamol/albuterol) will be provided as non-IMP to all subjects and labelled properly for clinical trial use only.

11.2. INVESTIGATIONAL MEDICINAL PRODUCT DISPENSING AND ADMINISTRATION

Subjects will administer the first dose of the IMP at the investigational site under the supervision of 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 CCI system, twice daily (morning and evening) over a period of 12 months. At least 10 minutes prior to each administration, an inhaled short-acting bronchodilator (e.g. salbutamol/albuterol) should be taken to improve tolerability. When the first dose is administered at the investigational site, subjects will have their FEV_1 monitored pre-bronchodilator and 30 ± 10 minutes post-IMP dose to investigate if there is any evidence of bronchospasm (defined as a decrease >15% in FEV_1 – not due to poor technique - from pre-bronchodilator baseline).

Subjects experiencing a decrease in FEV_1 >15% from pre-bronchodilator baseline and/or clinically determined bronchospasm after receiving their first dose of IMP, will be withdrawn from the trial.

The subject will administer the IMP at home twice daily (morning and evening) about at least 10 minutes after inhaled short-acting bronchodilator administration. If the patient does not wish to use the bronchodilator and tolerates the IMP without it, this is acceptable but should be documented appropriately.

The IMP must be reconstituted by carefully removing the red plastic cap on top of the vial and the attached aluminium collar seal, and injecting the 1 mL saline through the rubber stopper into the vial using a syringe provided by the CRO to each site. The vials must not be shaken but gently rolled between both hands to facilitate the dissolving of the powder. After 5 minutes of rest, the stopper can be opened and all of the solution transferred into the CCI chamber (with a 0.3 mL dosing chamber). Active treatment and placebo solutions are identical so that neither the Investigator nor the subject can recognize the identity of the product.

The instructions for preparation and administration of the IMP through the CCI device will be described in detail in an information leaflet for participating subjects.

The Investigator must instruct the subject to use the CCI device only for this study and only with the IMP provided. The IMP must not be diluted with any other solution or product.

At each visit, the subjects will be provided with sufficient IMP for treatment until the following visit including additional spare vials.

Subjects must be instructed to return the empty used and unused vials to the site at the respective visits. Subjects will be requested to bring their CCI to each clinic visit for the ongoing assessment of IMP adherence via the data analyser installed in the laptop provided by the Sponsor for this purpose.

11.3. RANDOMISATION

Each subject will receive a screening number as soon as site staff enters the IWRS, provided by CCI, after they have signed the Informed Consent Form (ICF) at Visit 1.

The screening number will consist of a country number (2 digits), a site number (3 digits) and a unique, sequential number for a subject at an individual site (3 digits), e.g. 01-001-001. Every subject who signs the ICF must be entered into the IWRS system regardless of eligibility.

At Visit 2, eligible subjects will be randomised using the 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 (azithromycin or erythromycin or clarithromycin) (Yes/No) will be considered for balancing randomisation. Thus, within each site, subjects with azithromycin or erythromycin or clarithromycin use will be randomised independently from subjects without use of azithromycin or erythromycin or clarithromycin, to receive colistimethate sodium or placebo in a 1:1 ratio.

The randomisation within each site and nested level of azithromycin or erythromycin or clarithromycin 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 17, the decision on whether stable concomitant antibiotic therapy with any oral macrolides (e.g. azithromycin/erythromycin/clarithromycin) will be administered to a subject or not will have been made at least 30 days prior to Screening (Visit 1). The treatment with oral macrolides should be continued throughout the trial in order not to jeopardize the study results.

The allocation to the treatment will be stored within the IWRS database until unblinding of the trial is requested. Unblinding may be performed through the IWRS directly by the Investigators only in case of SAE of life-threating significance where knowledge of treatment assignment is essential for the future management of patient care (see Section 13.1).

11.4. INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

IMP inventory and accountability records will be maintained within IWRS. The following rules are to be followed:

a) The Investigator will keep IMP in a pharmacy, or a locked and secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the IMP.

b) The inventory will be maintained by the Investigator or pharmacist or other nominated individual. A Site Inventory Summary Report will be printed from IWRS and signed by the Investigator or pharmacist and Clinical Research Associate (CRA) and filed in the Investigator Site File and/or Pharmacy Site File.

c) The IWRS includes details of IMP received and a clear record of when they were dispensed and to which subject and returned IMP and when returned. The IWRS shall indicate the quantity and description of all IMPs on hand at any time during the course of the clinical trial.

d) At the conclusion or termination of the clinical trial, the Investigator agrees to conduct a final IMP inventory and to record the results of the inventory on an appropriate form provided by the CRO/IWRS (Investigational Product Return Form). The pharmacist, if applicable, may assist with this. The monitor will check that IMP accountability was correctly performed. According to instructions, the Investigator will return all original IMP containers, whether empty or containing test preparations, to for final reconciliation and destruction.

e) The IMP can be dispensed to subjects only by the Investigator/pharmacist who agrees not to supply IMP to any person except those named as Investigators/Co-Investigators/study coordinators as detailed in the Site Signature/Delegation Log, and to subjects in this trial.

12. CLINICAL TRIAL AMENDMENTS

Changes to the CTP can only be made by preparing written amendments to be agreed and signed by the Investigator and Sponsor. No substantial amendment can be implemented without a favourable opinion of the EC and CA, unless the changes consist of urgent safety measures to protect trial subjects.

Amendments which are non-substantial amendments as defined by current regulations can be sent to the EC/CA for notification as applicable per local requirements, and may be implemented at the site before EC notification according to local rules.

13. DEVIATIONS FROM THE CLINICAL TRIAL PROTOCOL

Any major or critical deviation which may have an impact on study results and/or the safety of the subjects should be immediately reported to the CRO and a decision will be taken together with the Sponsor whether or not the subject (for whom the deviation from the CTP took place) is to continue in the trial. A deviation log will be maintained to track actual deviations and decisions taken, including all deviations which occurred. All deviations will be reported to the EC and CA according to ICH-GCP and local requirements.

In case of an emergency deviation from the CTP applicable only when an emergency situation has to be faced for a subject, this deviation will only be applied to that individual.

In such an emergency the Investigator must contact the CRO by telephone as soon as possible.

13.1. CODE BREAKING

The code for any individual subject will not be broken by the Investigator during the course of the trial except in the circumstance of an SAE where knowledge of treatment assignment is essential for the management of patient care.

In case of emergency, unblinding of the treatment code will be done through IWRS. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IWRS will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the site users. Site users will be provided with usernames and passwords to access the IWRS. Unblinding of the study treatment must be done in case of an emergency situation, where the Investigator considers it essential to know what treatment the subject was taking. Access to the unblinding option will be granted only to the Investigators and sub-Investigators at the sites. The IWRS will promptly notify the Sponsor and the CRA whenever a treatment code is unblinded. If the treatment code has been disclosed, this must be recorded in the eCRF.

Users from CCI and Sponsor Pharmacovigilance will have their own passwords to unblind subjects in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the CA and ECs.

14. CLINICAL TRIAL WITHDRAWALS/DROP-OUTS

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 (subject's follow-up should be performed in accordance with Section 16.9);
- 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, 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 eCRF as well as in respective source documents. Follow-up for withdrawn subjects follows the procedures described in Section 16.8 and Section 16.9. If possible, the subject should return to the clinic for an early End of Study Visit. The subject must return the medications, CCI, and details regarding AEs (including exacerbations) and concomitant medications will be collected.

15. STOPPING AND DISCONTINUATION CRITERIA FOR THE TRIAL

The trial may be prematurely terminated or placed on temporary hold for the following reasons:

- the Sponsor feels that the number and/or severity of AEs justifies discontinuation of the trial;
- the Sponsor considers the applied doses of the IMP to be no longer relevant;
- data not known before become available and raise concern about the safety of the IMP so that continuation would pose potential risks to the subjects.

Premature termination of the trial must be reported to the EC and CA according to applicable laws; generally within 15 days. A detailed written explanation of the reason should be given and alternative procedures for subjects under treatment specified.

However, trial results have to be reported according to the requirements outlined in this CTP as far as applicable.

If, after the termination of the trial, the risk/benefit analyses have changed, the new evaluation should be provided in case it will have an impact on the planned follow-up of the subjects who have participated in the trial. If possible, the subject should return to the clinic for an early End of Treatment Visit.

16. REPORTING SAFETY INFORMATION

16.1. DEFINITION OF ADVERSE EVENT

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

AEs include:

- worsening (change in nature, severity or frequency) of conditions present at the onset of the trial;
- subject deterioration due to the primary illness;
- intercurrent illnesses;
- drug interactions;
- events related or possibly related to concomitant medications;
- abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

16.2. DEFINITION OF ADVERSE EVENT OF SPECIAL INTEREST

No AEs of special interest are defined for this trial.

16.3. DEFINITION OF ADVERSE DRUG REACTION

An adverse drug reaction (ADR) is “any untoward and unintended response to an IMP related to any dose administered and which implies an AE with at least a reasonable possibility of a causal relationship with the use of the product (i.e. there is evidence or arguments to suggest a causal relationship).

The definition also covers medication error and uses outside what is foreseen in the CTP, including misuse and abuse of the IMP.

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as suspected ADRs.

16.3.1. DEFINITION OF UNEXPECTED ADVERSE DRUG REACTION

An unexpected ADR is: “An adverse reaction, the nature, or severity of which is not consistent with the applicable product information”.

The reference safety information for evaluation of AE expectedness in this trial will be Section 7.5.9 of the Investigator’s Brochure for colistimethate sodium in line with relevant information of the current EU SmPC Promixin® 1 MIU powder for nebuliser solution. In this patient population, pulmonary exacerbations (including pneumonia) are also considered as expected adverse events.

16.3.2. DEFINITION OF MEDICAL DEVICE MALFUNCTION AND INCIDENT

A medical device malfunction is the failure of a device to meet performance specifications or to perform as intended. A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, a user, or other persons, or to a serious deterioration in their state of health. A medical device complaint meeting the criteria of a potential medical device incident is reportable.

Subjects will also be monitored for any medical device malfunction or incident and, if these occur, details will be recorded as for ADRs.

16.4. DEFINITION OF SERIOUS ADVERSE EVENTS OR SERIOUS ADVERSE DRUG REACTIONS

16.4.1. DEFINITION OF SERIOUS ADVERSE EVENT OR SERIOUS ADVERSE REACTION

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening (i.e. the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement);

- is a congenital anomaly/birth defect;
- is an important medical event that may not result in death, be life-threatening, or require hospitalisation but, according to appropriate medical judgement, it may jeopardise the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

A Serious Adverse Reaction (SAR) is any SAE judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product.

16.4.2. DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

A Suspected, Unexpected Serious Adverse Reaction (SUSAR) is a subset of SAEs/SARs that, although foreseeable, are potentially related to the IMP and not identified in the reference safety information and will be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

16.5. DEFINITION OF SEVERITY OF ADVERSE EVENTS

The term “severe” is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the subject may experience slight discomfort;
- Moderate: causing some limitation of usual activities; the subject may experience annoying discomfort;
- Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

16.6. DEFINITION OF ADVERSE EVENT CAUSALITY

Causality shall be determined according to the definition of ADRs as given in Section 16.3.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as suspected ADRs. The causality assessment given by the Investigator should not be downgraded by the Sponsor.

The following binary decision for causality will be used:

- reasonable possibility that the IMP caused the event;
- no reasonable possibility that the IMP caused the event.

Features supportive of an association include:

- temporal plausibility;
- pharmacological properties of the drug or of the drug substance class;
- course of the AE after dechallenge and, if applicable, after rechallenge;
- specific tests indicating involvement of the drug in the occurrence/worsening of the AE;

- alternative explanations.

16.7. ADVERSE EVENT RECORDING

Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the IMP, must be recorded by the Investigator on the AE information page of the eCRF. Also, for SAEs, information must be recorded in the eCRF (see Section 16.8.1).

The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF.

16.8. ADVERSE EVENT REPORTING

The Investigator must report to the CRO all AEs which occur during the trial, regardless of their relationship to IMP. All AEs are recorded by the Investigator on the AE information page of the eCRF.

In addition, any SAE will have to be reported according to the following detailed procedure.

16.8.1. REPORTING SERIOUS ADVERSE EVENTS

Investigators must report SAEs **within 24 hours of first becoming aware of the event**.

The SAE must be reported through the eCRF to the CRO's Pharmacovigilance group as given in the contact details provided in the "List of Zambon/CRO personnel" at the beginning of this CTP.

If there is any issue with the electronic reporting process, such as internet failure or database issues, this must not delay SAE reporting. The back-up procedure is to send the back-up paper SAE Form to the CRO's Pharmacovigilance group by email or fax using the following contact details:

Email: CCI [redacted]

Fax: CCI [redacted]

Note: Any reports submitted on paper must be retrospectively added to the eCRF as soon as possible.

The community standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

SAEs are reportable from the time a subject signs the informed consent to the follow-up phone call 2 weeks after the last dose of IMP.

If the Investigator becomes aware of any SAE occurring to a subject within the follow-up window established in this CTP, he/she will report the SAE as above. The SAE will be also reported in the eCRF.

If the Investigator becomes aware of any SAE outside the follow-up window established in this CTP, it is the Investigator's responsibility to report the SAE to the CRO. The Investigator might use the eCRF, as described above. However, the SAE is not an event which occurred within the trial period.

16.8.2. REPORTING ADVERSE EVENTS OF SPECIAL INTEREST

No specific provisions relate to reporting of AEs of special interest.

16.9. FOLLOW-UP FOR ADVERSE EVENTS

All AEs requiring the subject's discontinuation and SAEs will be followed up until they are resolved or closed.

Resolution of an AE is defined as the return to pre-treatment status or stabilisation of the condition with the expectation that it will remain chronic.

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) and answer any question that the Sponsor or designee may have regarding the AE.

Regarding SAEs, the timelines and procedure for follow-up reports are the same as those for the initial reports for SAEs.

This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

If follow-up information on SAEs is available, a follow-up eCRF form will be filled-in by the Investigator and sent to the CRO as described above, under Section 16.8.1.

16.10. PREGNANCY

Subjects must be instructed that known or suspected pregnancy occurring during the trial should be confirmed and reported to the Investigator, who must then withdraw the subject from the trial without delay. This also applies in case the partner of a male subject becomes pregnant at any time during the whole course of the study (in this event a specific ICF for the subject's partner will be obtained).

In the event that a subject is subsequently found to be pregnant after inclusion in the trial, then the subject will be withdrawn from the study and the pregnancy will be actively followed up to term and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the CRO.

The Investigator will send pregnancy reports within the timeframes of SAEs.

If pregnancy results in an abnormal outcome that the Investigator and/or the Sponsor considers to be due to the IMP, this will be treated as an expedited ADR report.

17. RECORDS

17.1. CASE REPORT FORMS, SOURCE DATA AND QUERY RESOLUTION

The Investigator must ensure that the clinical data required by the CTP are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the official files (source documentation).

Data entered directly into the eCRF comprises all data recorded via the eCOA devices for CCI assessment, though an electronic copy of the subject's CCI data must be stored as source data at the investigational site at the end of the trial. If available, spirometry and ECG measurement results must be printed and signed by the Investigator and kept as source data on site after entering details into the eCRF. Adherence data from the CCI logging system will not be present at the investigational site as source data as they will be transferred into the eCRF from the sources directly. The Investigator will receive the results from the central lab by means of a laboratory report, and this should be signed by the Investigator, and stored as source data in the subject's file.

All other data has to be documented in the subject file as source data first and then entered into the eCRF.

Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a subject visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by trial monitors for completeness and acceptability during monitoring visits.

If data correction is required for an eCRF after initial entry, the site personnel can make necessary corrections on their own or as a response to an auto generated query by the eCRF system. The CRA and Clinical Data Manager review the eCRF for accuracy and can also generate queries to the investigational staff for resolution.

Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for the change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

17.2. RECORDS MAINTAINED BY THE INVESTIGATOR

A copy of all trial records (any documents sent or received from the Sponsor/CRO, correspondence with EC and any other institution or authority and relevant approvals, subjects' source data and subjects' identification documentation) must be maintained by the Investigator for at least 5 years (according to EU directive 2005/28/EC), or for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the Investigator.

17.3. TRIAL MASTER FILE

The Trial Master File (TMF) will be maintained electronically by the CRO according to the respective CRO SOPs with direct access for all CRO and Sponsor personnel.

At the end of the trial, the TMF will be transferred to the Sponsor, where it will be archived according to specific Sponsor SOPs. A copy of the Investigator files will be left on site after the end of the study.

17.4. TRIAL MONITORING

The trial will be monitored by means of regular visits and telephone calls according to specific and pre-defined SOPs and trial-specific monitoring guidelines. Details of the visits will be recorded in appropriate Monitoring Report forms to be submitted regularly to the Sponsor. Any relevant protocol deviation must be promptly communicated to designated Sponsor's personnel. Monitoring will be performed by personnel of the CRO, CCI [redacted].

17.5. CONFIDENTIALITY OF SUBJECT'S INFORMATION

The Investigator has the responsibility to maintain the anonymity of subjects in compliance with the Italian data protection law. In all trial documents, subjects are associated to a code

which does not reveal the subject's identity. Only at the site, the Investigator holds the subject's identity on a Subject Identification Log under his/her responsibility. The Investigator will maintain this for the longest period allowed by his/her own institution and, in any case, until further communication from the Sponsor.

The site and the Sponsor shall process personal data of subjects involved in the clinical trial as data controllers and in compliance with the Italian data protection law, each of them in its area of competence and in accordance with the responsibilities provided by GCP, only in relation to the trial performance and for pharmacovigilance purposes.

Any contracted organisation as data processor including the CRO, the central laboratory, eCOA provider, and IWRS provider, will act in compliance with the terms and conditions agreed with the Sponsor. All data will be handled in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data.

18. BIOMETRICS

18.1. DATA MANAGEMENT

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at the CRO.

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomisation, study drug supply
- Electronic Data Capture - eCRF
- eCOA device - CCI data capture
- Statistical Analysis System (SAS®) – statistical review and analysis
- Pharmacovigilance safety database

Subject data will be captured in an eCRF system and reviewed by the CRA in order to check CTP adherence and to detect any data inconsistency or discrepancy (data validation step).

Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version current at trial start and which will be maintained during the trial.

Previous and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

Actual versions of coding dictionaries used will be stated in the Clinical Trial Report (CTR).

The final data file will be transferred to the Sponsor in the agreed format as soon as possible after the trial is completed.

18.2. STUDY VARIABLES

Primary Efficacy Variable: The primary variable for this trial is the mean annual NCFB pulmonary exacerbation rate.

Secondary Efficacy Variables

- CCI [redacted]

Safety Variables

- incidence of TEAEs;
- absolute changes in percent-predicted FEV_1 from baseline (Visit 2) to end of treatment (Visit 7);
- number of subjects experiencing bronchospasm clinically or spirometrically determined following IMP administration at the start and end of treatment;
- CCI [redacted] from Screening/Randomisation (Visit 1/Visit 2) to Visits 3, 5 and end of treatment (Visit 7) as well as on CCI from Exacerbation Visits and clinic visits due to pneumonia;
- emergence of other bacterial colonies and any developing resistance in CCI 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.

18.3. SAMPLE SIZE

The sample size has been calculated considering the results from the previous trial CCI, relevant literature and the clinically meaningful benefit the treatment should provide. A treatment difference of CCI between the colistimethate sodium and placebo groups

For the purpose of the power calculation, a simulation of exacerbations has been carried out by randomly assigning a patient a value CCI according to the treatment group they are in and then generating a CCI event rate using this parameter. This CCI leads to two negative binomials with the following parameter values:

CCI
CCI .

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 Poisson regression allowing for over-dispersion for frequency of exacerbation (FOE), with a two-sided significance level of 0.05, a treatment effect of

CCI, and a follow-up time of CCI, assuming a frequency of CCI pulmonary exacerbations per annum for the FOE, a sample size of 170 completed subjects per group will provide a power of CCI

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

18.4. STATISTICAL ANALYSES

The statistical analysis will be performed by the CRO and it will be carried out according to 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 9.2 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.

Descriptive statistics will be used to present all efficacy and safety results: number of observations, mean, standard deviation, median, minimum, maximum for continuous data and frequency and percentage for categorical data. Statistics will be displayed by treatment group.

The analysis of the trial is on a comparative basis. Two-sided p-values <0.05 will be considered statistically significant and 95% two-sided confidence intervals (CIs) will be presented, where appropriate. Any adjustment for multiplicity will be detailed in the Statistical Analysis Plan (SAP).

More details about the statistical analysis will be provided in the SAP. The plan might be reviewed and updated as a result of the blind review of the data and will be finalised before breaking the blind. Any deviations from the SAP which occurred after breaking the blind will be documented and justified in the final CTR and deviations will be clearly marked as 'post hoc' analysis.

18.4.1. TRIAL POPULATIONS

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

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

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.

Primary analyses will be performed on the mITT population with exclusions from the ITT defined and justified in the SAP.

Following the ITT principle, 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 efficacy variables.

Safety Population

The Safety Population will comprise all subjects who provide Informed Consent 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 variables and demography.

Per-Protocol Population

The Per-Protocol Population (PP) will include all mITT subjects who were compliant with study drug administration (i.e. had a compliance 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 non-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; others will be defined in the SAP.

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

Exclusion of subjects from the PP analyses will be decided jointly by the CRO and Sponsor's Medical Monitor, Clinical Trial Manager and Statistician 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. Violations excluding subjects from any particular population will be described, reporting the number of protocol violators for each criterion. All protocol violations, minor ones included, will be listed.

18.4.2. EFFICACY DATA

The primary analysis will be performed on the mITT population. Analyses conducted using the PP will be considered supportive.

Primary Endpoint

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 A: there is no difference between inhaled colistimethate sodium and placebo as regards the effect on the pulmonary exacerbation rate against Alternative hypothesis A: inhaled colistimethate sodium reduces the pulmonary exacerbation rate.

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

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

- Cough

- CCI [redacted]

Mean Annual Pulmonary Exacerbation Rate

The number of NCFB pulmonary exacerbations during the treatment period will be analysed using a Poisson regression model allowing for over-dispersion including treatment, pooled sites and use of stable concomitant therapy with oral macrolides as fixed effects and log-time on trial as an offset.

The number and the percentage of subjects with NCFB pulmonary exacerbations, the number of pulmonary exacerbations and the total follow-up time in years will be summarised by treatment group. The adjusted yearly mean exacerbation rates in each treatment group and the adjusted rate ratio with their 95% CIs will be estimated by the model.

For the analysis, 2 pulmonary exacerbations will be considered as a single episode in cases where the second exacerbation starts less than 14 days after the end of the antibiotic therapy (oral or intravenous) for the first pulmonary exacerbation.

If the null hypothesis will be rejected, additional investigation of proportionality of the hazard will be implemented in a secondary analysis. Additional details on the analysis will be provided in the SAP.

A corresponding two-sided p-value of <0.05 will be considered statistically significant.

Secondary Endpoints

Summary statistics and analyses of the secondary efficacy/pharmaco-economic endpoints will be conducted for the mITT (main analysis) and the PP, as follows.

CCI [redacted] will be calculated as the time in days from the date of the first dose of IMP CCI [redacted] A log-rank sum test will be used to compare the treatment groups. Subjects completing the trial without CCI [redacted] or who are discontinued prematurely CCI [redacted], will be considered as censored at the time of their last follow-up.

CCI [redacted] will also be presented by treatment group. An appropriate non-parametric test will be used that makes allowing for the effect of prognostic covariates possible. This will be finalised in the SAP.

CCI

The number and the percentage of subjects CCI

CCI

CCI

The CCI total score and domain scores CCI will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2) will also be summarised for each post-baseline visit by treatment group. Scores will be computed according to the CCI manual [20].

Multiple entries and missing data will be dealt with as described in the same manual.

CCI 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 sites 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 at each visit will be estimated by the model.

The CCI will be summarised and analysed similarly to the CCI CCI Algorithm of scoring and methods for handling with multiple imputations and missing data will be performed according to the questionnaire instructions [21, 22].

CCI

The CCI as determined by the mean change in CCI from baseline (Visit 2) to Day 28 (Visit 3), as well as to Visits 5 and 7, will be compared between the treatment groups by an analysis of covariance model including treatment, pooled site 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-values will be estimated.

Sensitivity analyses may be conducted to assess the robustness of conclusions.

Summary statistics of the CCI CCI and change from baseline (Visit 2) will be provided by treatment group for each trial visit.

CCI

CCI

Absolute and relative frequency of subjects CCI CCI will be presented by treatment group along with the summaries for the CCI. Total number of days of CCI due to CCI per follow-up month will be collected during the study and described by treatment group.

18.4.3. SAFETY DATA

All safety endpoints will be summarised and analysed using the Safety Population.

Incidence of Treatment Emergent Adverse Events

The number and the percentage of subjects reporting TEAEs, treatment emergent SAEs, severe TEAEs, TEAEs leading to discontinuation and TEAEs leading to death will be presented by treatment group, along with the number of events occurring.

TEAEs will also be summarised by System Organ Class and Preferred Term according to MedDRA; they will additionally be summarised by severity and relationship to treatment. A separate summary table will be provided for SAEs.

Only TEAEs, i.e. events with an onset date on or after the date of IMP start, will be included in the summary tables. Individual data listings will include all AEs recorded; a separate listing will be provided for treatment-emergent SAEs.

Number of Subjects experiencing Bronchospasm Clinically or Spirometrically Determined following IMP Administration

The number of subjects experiencing bronchospasm spirometrically determined (a >15% decrease in FEV_1 - not due to poor technique - from pre-bronchodilator baseline in the 30 minutes post-IMP), or clinically determined, will be summarised by treatment. Percentages of subjects in each treatment group and the relative risk for colistimethate sodium group/placebo group will be provided with 95% CI. Treatment differences will be assessed using a Fisher Exact test.

The number and the percentage of subjects experiencing a bronchospasm following IMP administration as clinically determined will also be reported by clinical visit.

In addition, the results for FEV_1 and FVC at each visit will be summarised by treatment. Descriptive statistics for absolute and percentage changes from baseline, i.e. Visit 2 (pre-dose measurement) will be reported.

CCI [redacted]

The number and percentage of subjects whose CCI [redacted] at the end of treatment (at 12 months [Visit 7]) will be presented by treatment, overall and by status of previous usage of colistimethate sodium/colistin.

Vital Signs

Descriptive statistics for vital signs at Visit 1 and Visit 7 will be presented overall and by treatment.

Physical examination data

Descriptive statistics for physical examination data at Visit 1 and Visit 7 will be presented overall and by treatment.

Haematology, clinical chemistry and renal function tests

Haematology, clinical chemistry and renal function test results at Visit 1, Visit 5 and Visit 7 will be converted to standard international units and summarised by treatment group using descriptive statistics for continuous variables. Summaries for change from Visit 1 at Visit 5 and Visit 7 will also be provided. Renal function tests will also be summarised at Visit 3. Frequency of subjects with values appearing outside the central laboratory normal range will be reported by visit for each treatment group. All values appearing outside the laboratory normal range will be highlighted in listings.

12-lead Electrocardiogram

Descriptive statistics for ECG results will be presented overall and by treatment.

Adherence and Exposure

Subject adherence will be analysed based on the data collected by the CCI logging system.

Adherence will be summarised by treatment group presenting descriptive statistics and percentages of adherent subjects, i.e. with at least 80% adherence.

The total number of doses of IMP taken by each subject, as recorded as part of the CCI logging system will be summarised as well.

18.4.4. HANDLING OF MISSING DATA

Generally, there will be no imputation of missing values and only observed data will be included in the analyses.

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. In the AEs analysis, when relationship to study drug is missing for a TEAE it will be imputed to be drug related.

Additional details of handling of missing data for each type of analyses will be provided in the SAP.

19. INFORMED CONSENT

Written informed consent will be obtained by the Investigator or other authorised person from all subjects or their legally acceptable representative.

The Investigator is responsible for correctly obtaining the informed consent in accordance with the applicable regulatory requirement(s), GCP and the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, the Investigator must have received the EC written approval of the ICF.

Informed consent must be obtained prior to the initiation of any procedures specific to the trial. The record of the informed consent must be available to be audited/inspected by the Sponsor/CRO designees and by CA(s), whenever requested.

The informed consent documentation must be personally dated and signed by the trial subjects, to confirm that consent is based on information that has been understood, and by the Investigator.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

Before informed consent may be obtained, the Investigator or other authorised person, should provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject.

The subject should receive a copy of the signed and dated ICF and any other written information provided to him/her, and updates.

According to Directive 2001/20/EC, if the subject is not able to write, a verbal consent can be obtained. At least 1 impartial witness must be present during the obtaining of verbal informed consent.

Further, in case the subject and his/her legal representative are unable to read, informed consent will be obtained in the presence of an impartial witness, i.e. a person independent of the trial who will read the ICF and the written information for the subject.

20. ETHICS COMMITTEE APPROVAL

This trial will be undertaken only after written and dated approval from an appropriate EC has been received by the Investigator and by the Sponsor for the CTP, all its appendices, ICF, and subjects recruitment procedures (i.e. advertisement), if applicable.

In addition to the documents mentioned above, the EC will be provided with the Investigator's Brochure and any other documents that the EC may need to fulfil its responsibilities.

During the trial, on regular basis, the Investigator will have to submit written summaries of the trial status (i.e. recruitment rate) to the EC, if requested.

21. REGULATORY REQUIREMENTS

The trial is to be conducted in compliance with the European legislations (Directive 2001/20/EC and Directive 2005/28/EC) and the European Regulation 536/2014 and any applicable local regulations.

Selection of subjects will not start prior to the approval of the EC has been obtained and the trial notified to or authorised by CAs.

22. QUALITY ASSURANCE

This CTP has been audited by the Sponsor's Quality Assurance department. The Audit Plan for the study includes site audits. Audits will be planned and conducted according to the Sponsor's SOPs.

23. INSURANCE

The Sponsor is concerned with the safety of the subjects in the clinical trial and wishes to protect the Investigator (and, as applicable per local regulations, the site, the monitor and all the Investigator's staff involved in the trial) in the event of claims or lawsuits alleging injury as a result of administration of a study drug.

In consideration of undertaking a human trial in subjects according to this CTP the Sponsor will:

- indemnify the Investigator and hold him without liability for claims for damages arising out of the above described investigation in excess to those covered by his/her own professional liability insurance;
- defend the Investigator against any claims or lawsuits initiated by, or on behalf of, subjects who seek damages for bodily injury alleged to have been sustained as a result of administration of the study drug;
- pay any settlements of judgement resulting therefrom, providing that for all of the aforementioned cases, the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor;

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Indemnification is not valid for claims for damages arising from malpractice and/or negligence on the part of the Investigator or those under the Investigator's supervision.

The protection afforded by this policy does not take the place of the Investigator's professional liability insurance, but covers damages in excess of such insurance protection. Further, this indemnity is conditional upon the Investigator giving the Sponsor information as soon as reasonably practicable and upon the Investigator assisting the Sponsor and its authorised representatives in the investigation and defence of any suit for which coverage is provided.

24. CLINICAL TRIAL REPORT

A CTR of the trial will be prepared and written by the CRO according to ICH topic E3 (CPMP/ICH/137/95). A summary of the report will be sent to Investigators/EC/Regulatory Authorities according to current regulations.

25. USE OF INFORMATION AND PUBLICATION

The Investigator agrees to inform Zambon in advance about his/her intention to divulge any data, results concerning the Confidential Information and/or the trial subject to this agreement. As a consequence hereof, Investigator hereby undertakes to submit to Zambon, at least with a 60 days (30 days in case of abstracts) prior written notice, the text and/or the content of the concerned publication, sufficient to allow Zambon to properly assess that such proposed publication respects and/or is not in conflict with Zambon’s rights to preserve and protect its intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the trial is conducted.

Further, without any prejudice to Investigator’s right to divulge and save information for purposes stated herein-above, Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the trial hereto.

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27. APPENDICES

Appendix 1: Trial Flow Chart
Appendix 2: Investigator Signature Page

Appendix 1: Trial Flow Chart

ACTIVITIES (See sections 8 & 9 for details)	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
CCI		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 CCI **sample**	X	X		X		X		X		X
Spirometry: FEV_1 and FVC	X	X[b]		X	X	X	X	X[b]		X
CCI **training, dispensing/collection**		X						X		
Review of IMP administration & CCI **use (adherence)**		X	X	X	X	X	X	X		
Study medication: Dispense/accountability		X		X	X	X	X	X		
Record of CCI **and days of** CCI **due to pulmonary exacerbations**			X	X	X	X	X	X		X
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.

Appendix 2: Investigator Signature Page

I have read the attached protocol: 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*).

I agree to comply with the current International Council for Harmonisation Guidelines for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved.

I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred or if any proceeding for debarment is pending or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the EC.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

PROTOCOL AMENDMENT

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 Code: Z7224L01

Protocol Name: Promis I

EudraCT Number: 2015-002743-33

Date 18 Nov 2016 - Version Final 4.0

Date 31 Jan 2017 – Version Final 4.1 (UK only)

Date 03 July 2017 – Version Final 4.1 (Portugal only)

Date 17 Apr 2018 – Version Final 5.0

Date 12 Dec 2018 – Version Final 6.0

DATE/VERSION OF THE AMENDMENT: Version Final 7.0/22 Oct 2019

Zambon Spa
Via Lillo del Duca 10
20091 Bresso - Milan - Italy

Clinical Trial 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*)

APPROVALS:

As agreed and approved by:

23/10/2019 PPD

Date (dd/mmm/yyyy) **Dr** PPD **, Open R&D Global Head**

SIGNATURE

23/OCT/2019 PPD

Date (dd/mmm/yyyy) PPD **, Clinical Development Manager**

SIGNATURE

Summary of Key Changes		
Section Number & Title	Description of Change	Brief Rationale
Throughout	Minor administrative and formatting changes have been made to improve the quality of the overall study protocol document.	
Throughout	References to CCI [redacted]. have been amended to CCI [redacted] (the transitioning Contract Research Organisation [CRO]).	
Zambon Contact Details	The Medical Advisor details have been amended from Luca PPD to CCI	PPD has left Zambon SpA.
Contract Research Organisation Contact Details	The CRO details have been amended from CCI [redacted] to CCI [redacted], along with the associated Medical Monitors and contact details for Serious Adverse Event (SAE)/pregnancy reporting.	The CRO for the management of the study has been transferred from CCI [redacted]. to CCI [redacted]. This decision has been made following concerns regarding the ongoing management of the study and in order to improve audit preparedness.
Other Institutions	The details for CCI [redacted] have been deleted.	Central laboratory operations for Promis I do not include this division.
	The details for CCI [redacted] have been deleted.	The Investigational Medicinal Product (IMP) Packaging and Labelling operations for Promis I do not include this division.
Section 2: Summary; Trial Duration	The anticipated quarter for last subject out has been revised.	The date for last subject out has been amended to Q4 2020 to reflect the increased recruitment period required to achieve the required sample size.
Section 2: Summary; Population	Inclusion criteria #3 has been amended from “diagnosed with NCFB by computerised tomography (CT) or high-resolution CT (HRCT) as recorded in the subject’s notes” to “are diagnosed with NCFB by computerised tomography (CT) or high-resolution CT (HRCT) as recorded in the subject’s notes and this is their predominant condition being treated”.	Amended to emphasize and clarify that NCFB should be the predominant condition experienced by the study patient requiring treatment (as opposed to, for example, chronic obstructive pulmonary disease.
	Inclusion criteria #4 amended to allow patients experiencing 2 NCFB pulmonary exacerbations requiring inhaled antibiotics to be enrolled.	Discussions with sites have indicated that inhaled antibiotics are routinely being used at several sites and not just oral antibiotics as routine management for patients with NCFB pulmonary exacerbations.
	Inclusion criteria #7 has been amended to allow patients with a pre-bronchodilator FEV_1 ≥25% (as opposed to ≥30%).	The FEV_1 level has been adjusted downwards after consultation with experts in the field who agree this cut off level

		would not negatively impact the study in terms of safety but would help with recruitment.
	Inclusion criteria #8 has been amended to reflect the fact that any positive result for one of the three potential sputum samples collected during the periods between Visit 1 and Visit 2 allows for patient inclusion.	Amended to reflect the sputum sample collection details documented in relevant sections of the study protocol.
	Exclusion criteria #3 has been amended to remove the reference to myeloproliferative disease.	This was an exclusion criterion in the Zambon phase 2 trial but has not been an exclusion criteria in similar phase 3 trials. Removal of this exclusion criteria will have no negative impact on the safety of the trial or efficacy assessments. There are no known confounding factors with NCFB and myeloproliferative disease. Other exclusion criteria will ensure patient safety; in particular exclusion criteria #20 (as renumbered).
	Exclusion criteria #8 has been deleted in its entirety.	The amendment to inclusion criteria #3 detailed above makes this exclusion criterion redundant.
	Exclusion criteria #8 (as re-numbered) has been amended from “respiratory failure requiring long-term domiciliary oxygen therapy or non-invasive ventilation” to “respiratory failure that would compromise patient safety or confound the evaluation of safety or efficacy of the study in the opinion of the Investigator.”	The intention of the criteria was to exclude patients with respiratory failure who may not be fit enough to take part in a one-year trial. The use of oxygen or ventilation was a way of defining respiratory failure. Experience has shown that this is, in fact, confusing and patients using oxygen or night-time ventilation without respiratory failure were unnecessarily being excluded.
	Exclusion criteria #9 (as re-numbered) has been amended to include squamous cell carcinoma.	Localised squamous cell skin cancer (like basal cell carcinoma) does not pose a risk to the safety or efficacy assessments of the study.
	Exclusion criteria #10 (as re-numbered) has been amended to remove methotrexate.	Methotrexate does not have significant immunosuppressive properties.
	Exclusion criteria #12 (as re-numbered) has been amended from “current diagnosis or current treatment for non-tuberculous mycobacterial (NTM) pulmonary infection or tuberculosis” to “current treatment for non-tuberculous	Clarification of the intent of the exclusion criterion: amended for alignment with the ATS guidelines and the clinical study protocol for Promis I.

	mycobacterial (NTM) lung disease or tuberculosis".	
	Exclusion criteria #14 ("known to be intolerant to inhaled beta-2 agonists (bronchodilators") has been deleted.	This has been removed as Zambon have removed the absolute requirement to use a bronchodilator before each IMP administration. Zambon have removed this requirement due to feedback that, as many patients can tolerate the IMP without it, then the mandated use is an unnecessary burden on patients who would prefer not to use it. The use of the bronchodilator is to aid tolerability not to improve efficacy.
	Exclusion criteria #13 (as re-numbered) has been amended from "known or suspected to be allergic or unable to tolerate colistimethate sodium or other polymixins (intravenous or inhaled) including evidence of bronchial hyperreactivity" to "known or suspected to be allergic or unable to tolerate colistimethate sodium (intravenous or inhaled) or other polymixins, including evidence of bronchial hyper-reactivity following inhaled colistimethate sodium".	Clarification of exclusion criterion.
Section 2: Summary; Outcome Measures	The safety variable relating to bronchospasm has been extended to relate to any episode following IMP administration and not just at the end of treatment.	Clarification of the intention of the safety variable for the determination of any adverse effects.
	Testing for CCI [redacted] has been extended to all clinic visits at which CCI [redacted] samples are collected.	As some subjects may be considered eligible for the study based on local laboratory results for the presence of , additional central analyses at Visit 2 may capture some additional pre-existing resistance data. At Visit 3 we will also look at the susceptibility of to colistin sulphate. This is to identify if a pre-existing resistant strain present before commencement of IMP is growing preferentially if the IMP is suppressing the growth of susceptible strains. This will help differentiate from emergent resistance that may develop

		throughout the course of the study.
Section 3.1: Evaluation of the Anticipated Risks and Benefits	A statement has been added to allow patients to continue in the study without pre-bronchodilator use prior to IMP administration.	As stated above, this requirement has been removed due to feedback that, as many patients can tolerate the IMP without it, then the mandated use or a short-acting inhaled bronchodilator prior to IMP administration is an unnecessary burden on patients who would prefer not to use it. The use of the bronchodilator is to aid tolerability not to improve efficacy.
Section 6.1: Clinical Trial Design	The section has been amended to emphasize that any episodes of pneumonia should be followed up with clinic/'phone calls as per any pulmonary exacerbations.	As requested by the FDA, any episodes of pneumonia will be considered and followed-up in the same manner as pulmonary exacerbations.
Section 6.2: Duration of Clinical Trial	The anticipated quarter for last subject out has been revised.	The date for last subject out has been amended to Q4 2020 to reflect the increased recruitment period required to achieve the required sample size.
Section 7.2.1: Inclusion Criteria	Inclusion criteria #3 has been amended from "diagnosed with NCFB by computerised tomography (CT) or high-resolution CT (HRCT) as recorded in the subject's notes" to "are diagnosed with NCFB by computerised tomography (CT) or high-resolution CT (HRCT) as recorded in the subject's notes and this is their predominant condition being treated".	Amended to emphasize and clarify that NCFB should be the predominant condition experienced by the study patient requiring treatment (as opposed to, for example, chronic obstructive pulmonary disease.
	Inclusion criteria #4 amended to allow patients experiencing 2 NCFB pulmonary exacerbations requiring inhaled antibiotics to be enrolled.	Discussions with sites have indicated that inhaled antibiotics are routinely being used at several sites and not just oral antibiotics as routine management for patients with NCFB pulmonary exacerbations.
	Inclusion criteria #7 has been amended to allow patients with a pre-bronchodilator FEV_1 ≥25% (as opposed to ≥30%).	The FEV_1 level has been adjusted downwards after consultation with experts in the field who agree this cut off level would not negatively impact the study in terms of safety but would help with recruitment.
	Inclusion criteria #8 has been amended to reflect the fact that any positive result for one of the three potential sputum samples collected during the periods between Visit 1 and Visit 2	Amended to reflect the sputum sample collection details documented in relevant sections of the study protocol.

	allows for patient inclusion.	
Section 7.2.2: Exclusion Criteria	Exclusion criteria #3 has been amended to remove the reference to myeloproliferative disease.	This was an exclusion criterion in the Zambon phase 2 trial but has not been an exclusion criteria in similar phase 3 trials. Removal of this exclusion criteria will have no negative impact on the safety of the trial or efficacy assessments. There are no known confounding factors with NCFB and myeloproliferative disease. Other exclusion criteria will ensure patient safety; in particular exclusion criteria #20 (as renumbered).
	Exclusion criteria #8 has been deleted in its entirety.	The amendment to inclusion criteria #3 detailed above makes this exclusion criterion redundant.
	Exclusion criteria #8 (as re-numbered) has been amended from “respiratory failure requiring long-term domiciliary oxygen therapy or non-invasive ventilation” to “respiratory failure that would compromise patient safety or confound the evaluation of safety or efficacy of the study in the opinion of the Investigator.”	The intention of the criteria was to exclude patients with respiratory failure who may not be fit enough to take part in a one-year trial. The use of oxygen or ventilation was a way of defining respiratory failure. Experience has shown that this is, in fact, confusing and patients using oxygen or night-time ventilation without respiratory failure were unnecessarily being excluded.
	Exclusion criteria #9 (as re-numbered) has been amended to include squamous cell carcinoma.	Localised squamous cell skin cancer (like basal cell carcinoma) does not pose a risk to the safety or efficacy assessments of the study.
	Exclusion criteria #10 (as re-numbered) has been amended to remove methotrexate.	Methotrexate does not have significant immunosuppressive properties.
	Exclusion criteria #12 (as re-numbered) has been amended from “current diagnosis or current treatment for non-tuberculous mycobacterial (NTM) pulmonary infection or tuberculosis” to “current treatment for non-tuberculous mycobacterial (NTM) lung disease or tuberculosis”.	Clarification of the intent of the exclusion criterion: amended for alignment with the ATS guidelines and the clinical study protocol for Promis I.
	Exclusion criteria #14 (“known to be intolerant to inhaled beta-2 agonists (bronchodilators”) has been deleted.	This has been removed as Zambon have removed the absolute requirement to use a bronchodilator before each IMP administration. Zambon have removed this requirement due to feedback that, as many patients

		can tolerate the IMP without it, then the mandated use is an unnecessary burden on patients who would prefer not to use it. The use of the bronchodilator is to aid tolerability not to improve efficacy.
	Exclusion criteria #13 (as re-numbered) has been amended from "known or suspected to be allergic or unable to tolerate colistimethate sodium or other polymixins (intravenous or inhaled) including evidence of bronchial hyperreactivity" to "known or suspected to be allergic or unable to tolerate colistimethate sodium (intravenous or inhaled) or other polymixins, including evidence of bronchial hyper-reactivity following inhaled colistimethate sodium".	Clarification of exclusion criterion.
Section 8.2: Visit 2 - Randomisation Visit (Day 0)	Wording has been added to allow patients to continue in the study without pre-bronchodilator use prior to IMP administration.	As stated above, this requirement has been removed due to feedback that, as many patients can tolerate the IMP without it, then the mandated use or a short-acting inhaled bronchodilator prior to IMP administration is an unnecessary burden on patients who would prefer not to use it. The use of the bronchodilator is to aid tolerability not to improve efficacy.
	The timing for the administration of any pre-bronchodilator (at least 10 minutes prior to IMP administration) and post-IMP administration spirometry assessment (30 ± 10 minutes) have been amended.	The timings have been amended to reflect a more practical timeline and to indicate acceptable assessment ranges.
Section 8.5: Visit 7 (12 Months ± 1 Week); End of Treatment	The timing for the administration of any pre-bronchodilator (at least 10 minutes prior to IMP administration) and post-IMP administration spirometry assessment (30 ± 10 minutes) have been amended.	The timings have been amended to reflect a more practical timeline and to indicate acceptable assessment ranges.
	The reference to CCI devices being returned via CCI has been deleted.	This study procedure/logistic is not working effective and a new work instruction for the return of the CCI device is currently being created.
Section 9.1.6: Safety Evaluations	The timing for the spirometry assessments prior to the administration of any pre-	The timings have been amended to reflect a more practical timeline and to indicate

	bronchodilator (at least 10 minutes prior to IMP administration) and post-IMP administration (30 ± 10 minutes) have been amended.	acceptable assessment ranges.
Section 11.2: Investigational Medicinal Product Dispensing and Administration	A statement has been added to allow patients to continue in the study without pre-bronchodilator use prior to IMP administration.	As stated above, this requirement has been removed due to feedback that, as many patients can tolerate the IMP without it, then the mandated use or a short-acting inhaled bronchodilator prior to IMP administration is an unnecessary burden on patients who would prefer not to use it. The use of the bronchodilator is to aid tolerability not to improve efficacy.
	The timing for the administration of any pre-bronchodilator (at least 10 minutes prior to IMP administration) and post-IMP administration spirometry assessment (30 ± 10 minutes) have been amended.	The timings have been amended to reflect a more practical timeline and to indicate acceptable assessment ranges.
Section 17.8.1: Reporting Serious Adverse Events	The contact details for SAE reporting have been amended.	Contact details have been amended to those relating to the new CRO managing the study.
Section 18.2: Study Variables	Testing for CCI has been extended to all clinic visits at which CCI samples are collected.	As some subjects may be considered eligible for the study based on local laboratory results for the presence of CCI, additional central analyses at Visit 2 may capture some additional pre-existing resistance data. At Visit 3 we will also look at the CCI. This is to identify if a pre-existing resistant strain present before commencement of IMP is growing preferentially if the IMP is suppressing the growth of susceptible strains. This will help differentiate from emergent resistance that may develop throughout the course of the study.
Section 26: References	The date for the reference UK SmPC for Promixin has been amended from 2018 to 2019.	Annual update to the SmPC.
	The date the relevant web-site for the CCI reference was last known/accessed has been included.	The web-site no longer appears to be operational.