SAV008-01

An open-label, non-controlled, multicentre, pilot clinical trial of inhaled molgramostim in subjects with antibiotic-resistant non-tuberculosis mycobacterial (NTM) infection

NCT03421743

Clinical Trial Protocol

Version 4.0

04 October 2018

MOLGRAMOSTIM NEBULIZER SOLUTION

CLINICAL TRIAL PROTOCOL

SAV008-01

An Open-label, Non-controlled, Multicentre, Pilot Clinical Trial of Inhaled Molgramostim in Subjects with Antibiotic-resistant Non-tuberculosis Mycobacterial (NTM) Infection

OPTIMA

Product Name:	**Molgramostim Nebulizer Solution (Molgradex®) 300 µg**
Indication:	**Treatment-resistant pulmonary NTM infection**
Phase:	**IIA**
EudraCT No.	**2017-003374-14**
Sponsor:	**Savara ApS Slotsmarken 17, 2 t.v. 2970 Hørsholm Denmark**
Date of Protocol:	**04-Oct-2018**
Version:	**4.0**

2. SYNOPSIS

Name of Sponsor/Company:
Savara ApS

Name of Investigational Product:
Molgramostim nebulizer solution (Molgradex®)

Name of Active Ingredient:
Molgramostim (recombinant human GM-CSF)

Title of Study:
An open-label, non-controlled, multicenter, pilot clinical trial of inhaled molgramostim in subjects with antibiotic-resistant non-tuberculosis mycobacterial (NTM) infection

Study center(s): A sufficient number of centers located in Australia and United Kingdom

International Coordinating Investigator: Grant Waterer. Royal Perth Hospital, Australia

Studied period (years):	**Phase of development:**
Estimated date first subject screened: Q1 2018 Estimated date last subject completed (48 weeks treatment period): Q4 2019 Estimated date last subject completed (follow-up period): Q1 2020	IIA

Objectives:

Primary:

- To investigate efficacy of inhaled molgramostim on NTM sputum culture conversion to negative.

Secondary:

- To investigate efficacy of inhaled molgramostim on NTM sputum smear conversion to negative
- To investigate efficacy of inhaled molgramostim on reduction of NTM bacterial load in sputum
- To investigate efficacy of inhaled molgramostim on exercise capacity
- To investigate efficacy of inhaled molgramostim on Patient Reported Outcomes
- To investigate safety of inhaled molgramostim in subjects with NTM infection

Methodology:

A Screening Visit will be conducted up to 10 weeks prior to the Baseline Visit to determine eligibility. Adult subjects with a history of chronic pulmonary NTM infection with at least 2 positive cultures in the prior two years, of which at least one is within the last 6 months prior to Screening, will be considered for enrollment. Subjects should provide a positive sputum culture at Screening to be eligible.

Two subgroups of subjects will be recruited:

- Group 1: Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit
- Group 2: Subjects who remain sputum culture positive but have stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or who never started such treatment.

The study will include 30 subjects. The treatment period will consist of 14 trial visits (Screening, Baseline, and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 [visits at Weeks 28, 36 and 44 will include telephone contact, others will include clinic visits]) and a follow-up visit 12 weeks after end of treatment. At the Baseline Visit, eligible subjects will start treatment with inhaled molgramostim. At each visit, sputum samples for staining and microscopy, and microbiological culture will be collected. If required, induced sputum may be obtained according to local standards. Subjects will be asked to collect two additional sputum samples, preferably on the consecutive days after the clinic visit. For the visits at Weeks 28, 36 and 44 all three samples will be collected at home. In addition, clinical assessments including body weight, patient reported outcomes, and diffusing capacity of the lung for carbon monoxide (DLCO) will be conducted at each clinic visit. A computed tomography (CT) scan will be conducted at Baseline if not performed within 6 months prior to Baseline. In case of a drop in DLCO of at least 20% at two consecutive visits the CT scan may be repeated. A CT scan can be performed after 48 weeks of treatment if this is a part of the local routine clinical practice. Spirometry will be assessed at Baseline, and at Weeks 12, 24, 32, 40 and 48. A 6-minute walk test (6MWT) will be conducted at Baseline, at Weeks 12, 24, 48 and at the 12-week follow-up visit. Safety laboratory assessments will be assessed at Screening, Baseline and at Weeks 4, 12, 24, 32, 40, 48 and at the 12-week follow-up visit. Anti-GM-CSF antibodies will be assessed at Baseline, at Week 4, 12, 24, 32, 48 and at the 12-week follow-up visit. For subjects having a chest X-ray during the study period as part of the routine local clinical practice, the results from the X-ray will be recorded. Participating subjects will be encouraged to contact the clinic between visits if they experience adverse events (AE), worsening of their condition or have any other concerns.

Treatment with inhaled molgramostim will be given at a dosage of 300 µg once daily for 48 weeks. A data review was conducted after the first 6 subjects had completed 12 weeks of treatment. If safety concerns or poor tolerability were identified in this review, the review committee might decide on less frequent dosing for subsequent subjects in the study. The safety review concluded that there were no safety issues of significant concern and the dose was unchanged. In order to obtain more robust treatment responses, it was decided to extend the treatment duration to 48 weeks. If needed, unscheduled visits will be conducted at investigator's discretion.

During the study, subjects in Group 1 will continue use of antimycobacterial treatment. All changes in antimycobacterial treatment will be recorded, including reasons for each change. In case of worsening of NTM pulmonary disease, antimycobacterial treatment may be added or a dosage increase of antimycobacterial treatment may be applied as rescue treatment, according to investigator's discretion.

Number of subjects (planned):

30 subjects will be included. No formal sample size calculation was done as this is an initial pilot study.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. History of chronic pulmonary infection with *M. avium* complex (MAC) or *M. abscessus* (defined as at least 2 documented positive sputum cultures in the prior 2 years, of which at least one was obtained in the 6 months prior to Screening).
2. Subject fulfills one of the following criteria:
    - Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit
    - Subjects who remain sputum culture positive but have either stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or never started such treatment.
3. Ability to produce at least 2 mL of sputum or be willing to undergo an induction that produces at least 2 mL of sputum for clinical evaluation.
4. Female or male ≥18 years of age.
5. Females who have been post-menopausal for more than 1 year or females of childbearing potential after a confirmed menstrual period using a highly efficient method of contraception (i.e. a method with less than 1% failure rate such as combined hormonal contraception, progesterone-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence[1]), during and until thirty (30) days after last dose of trial treatment. Females of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at dosing at Baseline (Visit 2) and must not be lactating.
6. Males agreeing to use condoms during and until thirty (30) days after last dose of medication, or males having a female partner who is using adequate contraception as described above.
7. Willing and able to provide signed informed consent.
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures specified in the protocol as judged by the investigator.

[1] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Exclusion criteria:

1. Subjects diagnosed with cystic fibrosis.
2. Prior therapy with inhaled or systemic GM-CSF.
3. Subjects with hemoptysis of ≥60 mL in a 24 hour period within 4 weeks prior to Screening.
4. Concurrent disease with a life expectancy of less than 6 months.
5. History of, or present, myeloproliferative disease, leukemia or other hematological malignancy.
6. Active pulmonary malignancy (primary or metastatic); or any malignancy requiring

chemotherapy or radiation therapy within one year prior to Screening or anticipated during the study period.

7. Active allergic bronchopulmonary mycosis or connective tissue disease, inflammatory bowel disease or other autoimmune disorder requiring therapy associated with significant immunosuppression, such as systemic corticosteroids at a dose equivalent of 10 mg/day or more of prednisolone, within 3 months prior to Screening or anticipated during the study period.
8. Pulmonary tuberculosis requiring treatment or treated within 2 years prior to Screening.
9. HIV infection or other disease associated with significant immunodeficiency.
10. History of lung transplantation.
11. Any change in chronic NTM multi-drug antimycobacterial regimen within 28 days prior to Screening.
12. Treatment with any investigational medicinal product within 3 months of Screening.
13. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product
14. Any other serious medical condition which in the opinion of the investigator would make the subject unsuitable for the trial

Investigational product, dosage and mode of administration:

Investigational Medicinal Product (IMP): Molgramostim nebulizer solution

Active Substance: Molgramostim, recombinant human Granulocyte Macrophage Colony Stimulating Factor (rhGM-CSF)

Pharmaceutical form: Nebulizer solution

Route of administration: Inhalation

Inhalation device: PARI eFlow (PARI Pharma GmbH)

Duration of treatment:

Treatment will be given for 48 weeks.

Reference therapy, dosage and mode of administration:

Not applicable

Efficacy:

Primary Endpoint:

- Sputum culture conversion defined as at least three consecutive negative sputum samples during the treatment period.

Secondary Endpoints:

- Sputum smear conversion defined as at least three consecutive negative acid-fast bacilli (AFB) stained sputum smears on microscopy during the treatment period in subjects who were smear positive at Baseline.
- Durability of sputum culture conversion (defined as conversion at or before Week 48 and culture still negative at 12-weeks follow-up).
- Durability of sputum smear conversion (defined as conversion at or before Week 48 and smear still negative at 12-weeks follow-up).
- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.
- Change in semi-quantitative grade of sputum cultures from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.
- Change in symptom scores (assessed using Lower Respiratory Tract Infections – Visual Analogue Scale (LRTI-VAS) and Quality of Life Questionnaire– Bronchiectasis (QOL-B) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in Global Rating of Health (GRH) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in body weight from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in 6-minute walk distance (6MWD), oxygen desaturation and Borg CR10 scores during a 6MWT from Baseline to Week 12, 24, 48 and 12-week follow-up.

Safety:

- Number of adverse events (AEs), serious AEs (SAEs), adverse drug reactions (ADRs), severe AEs and AEs leading to treatment discontinuation during the trial period.
- Change in white blood cell counts (WBC) and differentials in blood from Baseline to Weeks 4, 12, 24, 32, 40, 48 and 12-week follow-up.
- Change in DLCO from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in forced expiratory volume in 1 second (FEV_1) (% predicted) and forced vital capacity (FVC) (% predicted) from Baseline to Weeks 12, 24, 32, 40 and 48.

Development of anti-GM-CSF antibodies at Week 4, 12, 24, 32, 48 and at 12-week follow-up.

Methods of Assessment

Microbiological characterization and quantification – Sputum culture will be done to confirm growth or absence of growth of NTM. In addition, a semi-quantitative assessment of bacterial load will be conducted.

AFB staining (fluorescence and/or Ziehl–Neelsen [ZN] stain) will be used to identify NTM in sputum and conduct a semi-quantitative assessment of bacterial load (graded as 0, occasional, 1+, 2+, 3+). Smears will also be fixated on slides and all slides will be submitted to a central laboratory for a second assessment.

Identification to NTM species level will be conducted on positive samples using established methods.

Routine bacteriology and fungal culture will be done on sputum samples.

Functional tests – A 6MWT test will be performed in accordance with European Respiratory Society/American Thoracic Society (ERS/ATS) guidance (2014). Borg CR10 scale will be used to assess dyspnea before and after the test.

Patient Reported Outcomes – clinical symptoms will be assessed using Lower Respiratory Tract Infections – Visual Analogue Score (LRTI-VAS), grading symptoms of dyspnea, fatigue, cough, pain, and sputum, Quality of Life Questionnaire– Bronchiectasis (QOL-B); and GRH which assesses global health as "excellent, good, fair or poor".

Radiology – if a chest X-ray or CT scan is done, information on the results will be collected.

Safety laboratory testing – A central laboratory will be used for analysis of hematology, clinical chemistry, and urinalysis.

Anti-GM-CSF antibodies – A central laboratory will be used for analysis of anti-GM-CSF antibodies

Pulmonary function testing – DLCO and spirometry will be done using local equipment. Percent of predicted values will be calculated centrally using standard equations.

Electrocardiogram (ECG) – ECG will be done using local equipment. No central overreading will be done.

Statistical methods:

Each subgroup (Group 1 and Group 2) will be analyzed separately. Data will be presented descriptively and using 95% confidence intervals. Statistical summaries comparing post-treatment values with Baseline will be conducted for selected endpoints. For the primary endpoint, (sputum culture conversion rates), the number of patients who convert to negative out of the number per group will be presented with 95% exact binomial confidence intervals.

As this is an exploratory study no adjustments for multiplicity will be done. Further details of all analyses will be given in the statistical analysis plan.

On the basis of the poor historical success rates of current standard therapy, a 30% response rate for the primary endpoint would be considered clinically relevant.

3. TRIAL FLOW CHART

Table 1: Study Schedule of Assessments

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[h]**	**V10**	**V11[h]**	**V12**	**V13**	**V14**	**V15**	**UV**
	Screening	**Base-line**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28 TC**	**Week 32**	**Week 36 TC**	**Week 40**	**Week 44 TC**	**Week 48**	**12-Week F-up**	**Unscheduled visit[a]**
Day		**< 10 wks after V1**	**28 days after V2**	**56 days after V2**	**84 days after V2**	**112 days after V2**	**140 days after V2**	**168 days after V2**	**196 days after V2**	**224 days after V2**	**252 days after V2**	**280 days after V2**	**308 days after V2**	**336 days after V2**	**84 days after V14**	
Window			**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Informed consent	X															
Eligibility criteria	X	X														
Demographics and body measurements	X															
Medical history	X															
Body weight		X	X	X	X	X	X	X		X		X		X	X	(X)
Prior and Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test and contraceptive check	X	X	X	X	X	X	X	X	(X)	X	(X)	X	(X)	X	X	(X)
Physical Exam	X							X						X		(X)
Vital signs	X	X	X		X			X		X		X		X		(X)

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[h]**	**V10**	**V11[h]**	**V12**	**V13**	**V14**	**V15**	**UV**
	Screening	**Baseline**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28 TC**	**Week 32**	**Week 36 TC**	**Week 40**	**Week 44 TC**	**Week 48**	**12-Week F-up**	**Unscheduled visit[a]**
Day		**< 10 wks after V1**	**28 days after V2**	**56 days after V2**	**84 days after V2**	**112 days after V2**	**140 days after V2**	**168 days after V2**	**196 days after V2**	**224 days after V2**	**252 days after V2**	**280 days after V2**	**308 days after V2**	**336 days after V2**	**84 days after V14**	
Window			**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
DLCO	X	X	X	X	X	X	X	X		X		X		X	X	(X)
Spirometry		X			X			X		X		X		X		
6MWT[b]		X			X			X						X	X	
Collection of Sputum sample	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	(X)
Laboratory Safety sampling	X	X[d]	X[d]		X[d]			X[d]		X[d]		X[d]		X	X	(X)
Sample for anti-GM-CSF		X[d]	X[d]		X[d]			X[d]		X[d]				X	X	(X)
ECG	X							X						X		(X)
Chest X-ray[e]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)	(X)	(X)
CT[f]		X												(X)		(X)
Questionnaires QOL-B, LRTI-VAS, GRH		X	X	X	X	X	X	X		X		X		X	X	(X)
Subject diary	X	X	X	X	X	X	X	X		X		X		X	X	
Trial drug administration training		X														(X)
Trial drug dosing at the site		X[g]	X[g]		X[g]			X[g]		X[g]		X[g]				(X)

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[h]**	**V10**	**V11[h]**	**V12**	**V13**	**V14**	**V15**	**UV**
	Screening	**Baseline**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28 TC**	**Week 32**	**Week 36 TC**	**Week 40**	**Week 44 TC**	**Week 48**	**12-Week F-up**	**Unscheduled visit[a]**
Day		**< 10 wks after V1**	**28 days after V2**	**56 days after V2**	**84 days after V2**	**112 days after V2**	**140 days after V2**	**168 days after V2**	**196 days after V2**	**224 days after V2**	**252 days after V2**	**280 days after V2**	**308 days after V2**	**336 days after V2**	**84 days after V14**	
Window			**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Dispense trial drug		X	X	X	X	X	X	X	(X)	X	(X)	X				(X)
Return of used trial drug			X	X	X	X	X	X		X		X		X		(X)
Compliance			X	X	X	X	X	X		X		X		X		(X)
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 6MWT= 6-minute walk test; AE=adverse event; CT= Computed tomography; DLCO= Diffusion capacity of the lung for carbon monoxide; ECG= electrocardiogram; GM-CSF=granulocyte macrophage colony stimulating factor; GRH=Global rating of health; LRTI-VAS= lower respiratory tract infection-visual analogue scale; QoL-B= Quality of Life- Bronchiectasis

[a] Procedures marked with brackets should be performed as necessary.

[b] 6MWT includes assessment of SpO_2 and Borg CR10 score for dyspnea before, during (SpO_2) and after (Borg) the test.

[c] Three samples, preferably on consecutive days, will be collected. All samples collected at V9, V11 and V13 will home collected.

[d] Sample to be taken before dosing at the site.

[e] A chest X-ray not a study requirement. But if subjects have a chest X-ray during the study period as part of the local routine clinical practice, the results from the X-ray will be recorded.

[f] A CT scan performed up to 6 months prior to the Baseline visit is accepted. A CT scan can be performed at V14 if this is a part of the local routine clinical practice.

g Trial drug dosing should be performed after blood sampling.

h Visit 9 and 11 can be scheduled as a site visit if deemed necessary by the investigator. Procedures in brackets should be performed if visit 9 or 11 is performed as a site visit.

4. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6MWT	6 Minute Walk Test
6MWD	6 Minute Walk Distance
aPAP	Autoimmune Pulmonary Alveolar Proteinosis
ADR	Adverse Drug Reaction
AE	Adverse Event
AFB	Acid Fast Bacilli
anti-GM-CSF	Antibodies Towards Granulocyte Macrophage Colony Stimulating Factor
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Concentration Versus Time Curve
BAL	Bronchial Alveolar Lavage
CA	Competent Authority
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organization
CRP	C-Reactive Protein
CT	Computer Tomography
CTR	Clinical Trial Report
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFD	Embryo Fetal Development
EVF	Erythrocyte Volume Fraction
eGFR	Estimated Glomerular Filtration Rate

Abbreviation or Specialist Term	Explanation
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMP	Good Manufacturing Practice
GRH	Global Rating of Health
IB	Investigator's Brochure
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IDSA	Infectious Diseases Society of America
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
LRTI-VAS	Lower Respiratory Tract Infections – Visual Analogue Scale
MAD	Multiple Ascending Dose
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
NK	Natural Killer Cells
NOAEL	No Observed Adverse Effect Level
NTM	Non -Tuberculosis Mycobacteria
NTM-PD	Non -Tuberculosis Mycobacteria Pulmonary Disease
PCR	Polymerase Chain Reaction
PCV	Packed Cell Volume
PCV/EVF	Packed Cell Volume (PCV) Or Erythrocyte Volume Fraction (EVF) Also known as Hematocrit
PT	Preferred Term

Abbreviation or Specialist Term	Explanation
PT-INR	Prothrombin Time International Normalized Ratio
QoL-B	Quality of Life- Bronchiectasis
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
rhGM-CSF	Recombinant Human Granulocyte Macrophage Colony Stimulating Factor
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Blood Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Time of Maximum Plasma Concentration
VC	Vital Capacity
WBC	White Blood Cells
WHO	World Health Organization
ZN	Ziehl–Neelsen stain

6. INTRODUCTION

6.1. Background

Non-tuberculosis mycobacterial (NTM) infection

Pulmonary disease due to NTM is an increasing problem in the USA and most western countries. Over the last three decades an increasing incidence of pulmonary NTM isolation has been observed [Wassilew 2016, Stout 2016] and NTM are now recognized to be a major cause of chronic lung disease. Non-tuberculosis mycobacteria cause progressive lung destruction resulting in a variety of symptoms including cough, breathlessness and weight loss.

Incidence rates of NTM pulmonary disease (NTM-PD), show wide geographic variation. In Queensland, Australia with compulsory reporting of NTM-PD, the prevalence in the general population was 15.1 per 100,000 in 2010 [Thomson 2015]. In Europe prevalences ranging from 0.2 to 2.9 per 100,000 have been reported [Wassilew 2016] and across the USA prevalences range from 1 to 10 per 100,000 [Stout 2016]. In Ontario, Canada the annual prevalence of disease was reported as 9.8 per 100,000 [Marras 2013]. Disease frequency increases markedly with age [Winthrop 2011]; the prevalence in the over 65 age group was reported as 47 per 100,000 in 2007, an increase from 20 per 100,000 in 1997 (corresponding to an 8.2% yearly increase) [Adjemian 2012]. In Germany, the highest prevalence rates were observed among patients >50 years of age, in particular among those ≥80 years of age (9.4 and 9.6 per 100,000 for men and women respectively) [Ringhausen 2016]. In the USA, consistent with findings in Germany, disease frequency increased markedly with age, with prevalence of 15, 30 and 57 per 100,000 observed in age groups ≥60 years, aged 70-79 years and ≥ 80 years respectively [Prevots 2010]. Studies of patients with bronchiectasis in the USA suggest almost two-thirds have NTM-PD [Aksamit 2017], suggesting rates are likely to be in the order of per 200-300 per 100,000 in the over 65 age group. Several factors may contribute to the emergence of NTM-PD, including an aging population with chronic lung diseases, advances in microbiological techniques and radiological diagnostics that have improved the identification of pulmonary abnormalities [Wassilew 2016, Stout 2016].

Although over 160 species of NTM cause human disease, the most in common the USA are *M. avium* and *M. intracellulare*, and, in a few regions, *M. kansasii*. *M. abscessus* is also a problem in the USA as it is a much more aggressive infection than other NTM with worse patient outcomes and requiring intravenous and oral therapy. While NTM are nothing like as contagious as tuberculosis, they are transmissible from human to human, [Aitken 2012] and in the case of *M. abscessus* this may be the major route of acquisition [Bryant 2016].

Successfully treating NTM disease is a major problem for clinicians and patients. Antibiotic options for NTM are poor [Griffith 2007, Griffith 2016]. The standard regime for NTM (avium, intracellulare and kansasii) is a 3-drug regimen of a macrolide (clarithromycin or azithromycin), a rifamycin (usually rifampicin) and ethambutol. In clinical trials, it is usual for more than half of patients to describe significant side effects of therapy, with up to a quarter being intolerant of therapy [Griffith 2007, Aksamit 2017, Rawson 2016]. For this reason, the intention to treat cure rates in clinical trials are usually no more than 50%. Clinical experience is that 'normal' practice outside of clinical trials is much worse than this. [Rawson 2016] Typical side effects are severe

nausea, vomiting, diarrhea, peripheral neuropathy, hepatitis, skin rashes, blood dyscrasias, visual loss and hearing loss. Treatment is usually for a minimum of 18 months, or at least 1 year after the last positive sputum culture (which is rarely in the first 6 months of therapy) [Griffith 2007].

Follow up studies of clinical trials in NTM show that within 3-years up to half of patients have disease recurrence. This is a mixture of reactivation of prior disease and acquisition of new NTM from the environment [Lam 2006]. Non-tuberculosis mycobacteria do progressively acquire drug-resistance, including to rifampicin, amikacin, macrolides and quinolones [Cowman 2016, Zhao 2014, Heidarieh 2016]. The presence of macrolide resistance is well established to be associated with worse patient outcomes [Griffith 2016]. For this reason, subsequent episodes of disease become progressively harder to treat and some means of preventing disease after apparent cure is desperately required [Griffith 2016].

Investigational Medicinal Product (IMP)

The IMP, Molgramostim nebulizer solution, is developed by Savara Pharmaceuticals. The drug substance molgramostim (rhGM-CSF) is produced in *E. coli* and has the same amino acid sequence as the native protein but is not glycosylated. Another rhGM-CSF product, sargramostim, which is produced in *S. cerevisiae* slightly differs from native GM-CSF by having one amino acid difference in position 23 and is glycosylated. Production of molgramostim in bacteria circumvents the variability in the molecular weight seen in sargramostim. The formulation currently under development is intended for inhalation use.

No rhGM-CSF products have been approved for respiratory disease therapy or for inhalation use in any indication. Two rhGM-CSF products for systemic use have been approved, *E.coli* derived molgramostim (Leucomax®) and yeast-derived sargramostim (Leukine®), largely for use following chemotherapy and/or bone marrow transplantation to reduce the risks of neutropenia such as infection, or in case of graft failure after bone marrow transplantation. Published clinical studies of relevance to the development of molgramostim nebulizer solution in which investigational or commercially available rhGM-CSF products have been administered are summarized and discussed in the Investigator's Brochure (IB).

Pre-clinical studies in cynomolgus monkeys show that molgramostim is deposited in the lungs after inhalation. The small fraction of the inhaled dose that is absorbed systemically causes increases in stem cell proliferation, resulting in increased number of monocytes, eosinophils and neutrophils in the circulation; similar to the known effects after intravenous (IV) administration of rhGM-CSF.

Toxicity of inhaled molgramostim nebulizer solution was investigated in cynomolgus monkeys, as this is the most relevant animal species for safety evaluation. After inhalation of molgramostim nebulizer solution, rhGM-CSF is deposited in the lungs. Local effects in the lungs are characterised by accumulation of inflammatory cells, mostly macrophages, accompanied by an increased cellularity in the lymphoid tissue that is associated with the respiratory tract and minimal to mild exudation of red blood cells into the alveoli. The infiltration of inflammatory cells was not associated with any signs of inflammation or impaired lung function, and it is interpreted as an exaggerated pharmacological effect of molgramostim. Its severity was graded slight at the 10 µg/kg/day dose level and moderate above this level. Duration of treatment did not affect the severity of this finding. Reduced severity of the lung and tracheobronchial changes following 4 weeks off dose in recovery animals suggests partial resolution of the changes.

Bronchopneumonia was found in one monkey treated with 42 µg/kg/day and in one treated with 127 µg/kg/day, both from the same study, which employed a bronchoalveolar lavage (BAL) procedure before treatment. Since bronchopneumonia is a well-known sequela of BAL and because no bronchopneumonia was reported from any animal in studies that did not include this pre-treatment procedure, it was concluded that the bronchopneumonia was not directly related to molgramostim nebulizer solution.

The No Observed Adverse Effect Level (NOAEL) across all inhalation toxicity studies was based on the chronic (26-week) inhalation toxicity study and was set at the 40 µg/kg/day nominal dose level. NOAELs from other toxicity studies than the 26-week study was either at the same nominal dose level (i.e. the 13-week study) or at a higher nominal dose level (i.e. the 6-week study).

Safety margins for local lung burden, that derive from the NOAEL at 40 µg/kg/day and that take into consideration the differences in lung deposition between monkeys and man, are around 7 for a clinical dose of 300 µg per subject. Safety margins based on a comparison of the plasma area under the concentration versus time curve (AUC) between monkeys (at the NOAEL) and volunteers from a phase I clinical trial are around 8 for a clinical dose of 300 µg per subject.

An embryo-fetal developmental (EFD) toxicity study with molgramostim nebulizer solution has been conducted in rabbits, which show a similar pharmacological response as humans or monkeys, although at a lower potency. The EFD study revealed increases in post implantation loss, decreases in the number of live implants, effects on sex ratio and a slight increase in the incidence of major malformations in fetuses at the highest dose (150 µg/kg/day), consistent with findings from other rhGM-CSF products. Studies in sexually mature monkeys have shown that molgramostim has no effect on male and female reproductive organs.

Further details are available in the Investigator's Brochure (IB).

The first clinical study with molgramostim nebulizer solution has been completed (MOL-001). This was a phase I study to investigate the effects of molgramostim nebulizer solution in healthy adult subjects. The study was a randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in 42 adults; non-tobacco using male and non-child bearing female subjects. In the SAD part, 18 subjects were included with four subjects in each of the three SAD dose levels (150 µg, 300 µg and 600 µg) and six receiving placebo. In the MAD part, 24 subjects were included with nine subjects in each of the two MAD dose levels (300 µg or 600 µg) and six receiving placebo once daily for six days.

All 42 subjects enrolled completed the study. GM-CSF was not measurable in serum before study drug administration. In the SAD part, GM-CSF was absorbed into systemic circulation with time of maximum plasma concentration ($t_{max)}$ of 2 hours after inhalation of molgramostim nebulizer solution, however, at picogram levels 50-100 times lower than has been observed after similar doses of sargramostim administered intravenously. Total systemic exposure (AUC_{last}) increased with dose ranging between 13 and 138 pg•h/mL and maximum measurable plasma concentrations (C_{max}) ranged between 9.1 and 41 pg/mL (C_{max} was similar for the 300 and 600 µg dose levels). In the MAD part, despite the short half-life of approximately 4 hours where GM-CSF levels returned to levels below quantification limits after each dose, there was evidence of some accumulation after multiple dosing. C_{max} increased from 32 pg/mL on Day 1 to 90 pg/mL

on Day 6 for the 300 μg dose level and from 96 pg/mL to 251 pg/mL from Days 1 to 6 for the 600 μg dose level. Likewise, AUC_{last} increased from 97 to 248 pg•h/mL from Days 1 to 6 for the 300 μg dose level and from 350 to 802 pg•h/mL for the 600 μg dose level. Minimum measurable plasma concentrations (C_{min}) on Day 6 were 3.6 and 5.1 pg/mL measured at 8 and 12 hours, respectively for the 300 and 600 μg dose levels.

Changes in white blood cells (WBC) and differential counts were in-line with the mode-of-action of GM-CSF and these were not clinically significant in most subjects. In subjects treated with molgramostim nebulizer solution a slight increase in total WBC and differential counts (primarily within normal reference ranges) was observed in a dose-dependent manner. Two subjects had adverse events (AEs) concerning WBC differential counts that were considered related to GM-CSF (eosinophilia and white blood cell count increased).

The most common AE was cough, reported for 21/30 (70%) subjects receiving molgramostim nebulizer solution and 8/12 (67%) receiving placebo. The AEs considered treatment-related reported by two or more (>5%) subjects receiving molgramostim nebulizer solution were: cough (50%), productive cough (10%) and headache (6.7%). Cough was considered treatment-related for a similar proportion of subjects receiving placebo (58%). Number of cough events were 48 in 30 subjects in the combined molgramostim groups and 15 in 12 subjects in the placebo groups. A higher number of treatment-related AEs were observed in the 600 μg dose level compared to the 300 μg dose level and placebo in the MAD part. There was no development of anti-drug antibodies up to 28 days after last dose. There were no serious adverse events (SAEs), severe AEs, dose-limiting toxicity, or other remarkable findings of clinical concern from review of clinical safety data.

Further details are available in the Investigator's Brochure (IB).

Two clinical studies with molgramostim nebulizer solution are currently ongoing. Study MOL-PAP-002 is a pivotal clinical trial in autoimmune pulmonary alveolar proteinosis (aPAP) being conducted in Europe, Japan, Israel, Russia, Turkey, South Korea, and Australia. This trial is a randomized, double-blind, placebo-controlled trial, planned to enroll 90 patients with aPAP. Treatment is given for 24 weeks and consists of daily administration of molgramostim nebulizer solution 300 μg, alternating cycles of molgramostim nebulizer solution 300 μg daily for 7 days and placebo daily for 7 days or daily administration of placebo. After the double-blind period, there is a 24- to 48-week follow-up period, during which open-label treatment with molgramostim nebulizer solution is given. Three reviews of unblinded safety data by an independent data safety monitoring board (DSMB) have been conducted, including 10, 38 and 59 randomized patients, respectively. Data reviewed comprised adverse events, safety laboratory data, vital signs and pulmonary function tests from up to 60 weeks of treatment. No safety signals of concern were identified and the DSMB recommended that the trial could continue as planned.

Further details are available in the IB.

6.2. Trial Rationale

As NTM are inherently resistant to antibiotics treatment is difficult, typically requiring at least three antibiotics for a minimum of 18 months. Discontinuation of treatment due to adverse drug effects is frequent (10–30%), and the overall treatment success rate is only 40–60%. The treatment success rate is higher (70–85%) in patients with non-cavitary nodular bronchiectatic lung disease than in those with cavitary lung disease. Even after successful completion of antibiotic therapy, microbiological recurrence (predominantly due to reinfection rather than relapse) is relatively common (30–50%), especially in patients with nodular bronchiectatic lung disease [Stout 2016]. Thus, new treatments are urgently required. The current study is a pilot study in subjects who have not responded to multidrug NTM guideline based antimycobacterial regimens in the past for reasons of lack of efficacy, inability to tolerate the drug regimen, or did not want to take it. Response to further NTM treatments in this subgroup would be not expected.

Due to their thick cell wall and resistance to normal extracellular defense mechanisms, successful killing of mycobacteria requires phagocytosis by macrophage. The macrophages then recruit additional help in the form of T-lymphocytes and Natural Killer (NK) cells, which in turn activate the macrophage so that it develops sufficient lysosomal activity to neutralize the bacteria [Awuh 2017]. At the same time mycobacteria have developed a variety of strategies to not only survive within macrophages, but to feed off their lipid-rich environments, multiply and ultimately lyse the host cell and spread further within the host. In NTM disease the fundamental problem is failure of this macrophage containment and neutralization [Awuh 2017].

While many immune defects have been described in patients with NTM including genetic abnormalities in interferon-gamma, interleukin-12 and their receptors, anti-cytokine antibodies including anti-GM-CSF and deficient response to interferon-gamma, none have consistently been identified in patient cohorts [Stout 2016]. It is therefore likely that there are a variety of host defects that predispose patients to NTM disease with a common end pathway being impaired macrophage function.

An ideal new therapy would 1) reverse the primary problem of deficient macrophage killing capacity, 2) not have the capacity to generate resistance and 3) preferably act synergistically with existing antibiotic approaches to allow either less antibiotics, lower doses that may be better tolerated, or both, and prevent reinfection in vulnerable hosts.

GM-CSF is a glycoprotein secreted by macrophages, T cells, mast cells, NK cells, endothelial cells and fibroblasts in response to a variety of inflammatory cytokines including tumor necrosis factor alpha, interleukin-1 and interleukin-12 [Fleetwood 2005]. Activation of the GM-CSF receptor stimulates at least three pathways – JAK-STAT, MAPK and PI3K [Fleetwood 2005] and has been used extensively in oncology due to its ability to stimulate stem cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes. In the lung GM-CSF increases the number of macrophages with smaller increases in the number of neutrophils, basophils and eosinophils [Rose 1992]. Unlike macrophage colony stimulating factor (M-CSF), GM-CSF also increases the activation of macrophages, resulting in greater phagocytic and cytotoxic activity [Fleetwood 2005]. The pivotal role of macrophages as the effector cell in immunity to mycobacteria has long been established [Martino 2008].

There is substantive animal in-vivo and human in-vitro data supporting GM-CSF as a therapy for NTM infection as both a sole agent and as a potentiator of antibiotic therapy. GM-CSF alone is

sufficient for inhibition of mycobacterial growth in mouse macrophages, demonstrating the key "end effector" function of GM-CSF [Rothchild 2014]. Also, GM-CSF as mono-therapy has been shown to be capable of controlling NTM infection in animal models and human macrophage cell lines [Onyeji 1995, Bermudez 1994]. GM-CSF potentiates the effect of antibiotics against NTM, probably through increasing intra-macrophage concentrations of antibiotics which are dependent on active transport into the cell [Onyeji 1995, Bermudez 1994]. Furthermore the antibiotic-potentiating effect of GM-CSF has been shown in Leishmaniasis [Almeida 1999] and Pseudomonal infection [Choudhary 2015].

Clinical data demonstrating successful treatment of NTM disease with rhGM-CSF are also available. During the AIDS epidemic, the administration of parenteral rhGM-CSF was reported to control systemic NTM infection resistant to antibiotic therapy and increase anti-mycobacterial acitivity [de Silva 2007, Kemper 1998, Kedzierska 2000]. Two cases of adult patients with cystic fibrosis and *M. abscessus* disease non responsive to conventional antibiotic therapy for more than 12 months have been reported to respond to rhGM-CSF. [Moser 2005]. Supportive data from interferon gamma, which acts through the GM-CSF pathway, are also available. A published case report of inhaled interferon-gamma in a patient with drug resistant *M. avium* infection demonstrated microbiological cure within 7 months and a reduction in sputum counts within 2 months [Hallstrand 2004]. A second case of *M. avium* with no improvement after 3-years of 3-drug therapy showed reduced levels of NTM in sputum during two 5-week courses of inhaled interferon gamma and became smear negative during the third course [Chatte 1995]. Intramuscular interferon gamma was given for up to 6 months as adjuvant to antimycobacterial multidrug therapy in a placebo-controlled study in 32 patients with atypical mycobacterial infections, mainly MAC. Interferon gamma showed trends of improvements in clinical, radiological and microbiological parameters over placebo [Milanes-Virelles 2008]. As GM-CSF is the most potent effector of macrophages induced by interferon gamma, a similar marked and rapid improvement in disease may be expected.

Clinical data have also shown that rhGM-CSF is well tolerated when inhaled. Given that anti-GM-CSF therapies have been trialed for asthma, chronic obstructive pulmonary disease (COPD) and autoimmune diseases there is some theoretical risk these may be exacerbated or precipitated. However as previously noted there is minimal systemic absorption of rhGM-CSF from inhalation and as below there are no current reports of adverse effects. In animal studies as well as in the human phase I study there were no significant adverse effects including no increase in airways reactivity. Clinical experience in using inhaled molgramostim in the setting of alveolar proteinosis has so far recorded no serious adverse drug reactions in more than 60 patients enrolled through the current clinical development program. Lastly there are very limited reported side effects of inhaled rhGM-CSF despite case reports and small studies detailing its effectiveness in close to 100 patients in the setting of alveolar proteinosis.

In the current study, the patient population are adult subjects with persistent pulmonary NTM infection as evidenced by at least two positive sputum cultures in the prior two years, one of which within the 6 months prior to Screening, and a positive culture at Screening. A population of treatment-resistant, treatment-intolerant, or never treated patients was selected as these are the patients who are currently not well-treated with current standard multidrug antimycobacterial regimens. In order to obtain pilot data on the possible scenarios where the medical need is considered to be the highest, (i.e. subjects who can tolerate standard antimycobacterial treatment but remain NTM positive despite continued treatment, or subjects who are not treated because

they have given up on treatment, could not tolerate treatment or did not want to start treatment) subjects will be stratified into two groups as follows:

- Group 1: Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit.
- Group 2: Subjects who remain sputum culture positive but have either stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or never started such treatment.

Although there are very successful case reports of the use of GM-CSF in patients with cystic fibrosis, these patients will be excluded as these patients, unlike the normal setting of NTM infection, typically have multiple pathogens identified at the time of NTM isolation.

In this trial, molgramostim will be administered via inhalation using PARI eFlow nebulizer system (PARI Pharma GmbH, Germany) which is consistent with the pivotal study in aPAP (MOL-PAP-002). The dose of 300 μg once daily is the same dose as currently being used in the pivotal study in aPAP (MOL-PAP-002). A data review was conducted after the first 6 subjects had completed 12 weeks of treatment. If safety concerns or poor tolerability were identified in this review, the review committee might decide on less frequent dosing for subsequent subjects in the study. The review was conducted on 16 September 2018 and concluded that there were no safety issues of significant concern and the dose was unchanged. In order to obtain more robust treatment responses it was decided to extend the treatment duration to 48 weeks.

6.3. Potential Risks and Benefits

Although the clinical case report data is extremely encouraging, the true response rate to GM-CSF in NTM infection is unknown. This pilot study is intended to gather the detailed data relevant to planning of the further phase II program, to be conducted in the more formal setting of a randomized, double-blind clinical trial.

As outlined above, pulmonary NTM disease is now a major problem and is increasing, treatment is poorly tolerated, is often ineffective and even successful therapy is associated with recurrence rates of 50% within 3 years. Patients urgently need better therapies.

As the majority of inhalational use of rhGM-CSF has been in the context of PAP, where patients have pre-existing anti-GM-CSF antibodies, it cannot be excluded that there will be more adverse effects in the treatment of NTM infection due to higher local and systemic exposure. The safety monitoring in the study has been selected to address these aspects.

To ensure adequate subject safety in this pilot study, a data review was conducted by a review committee (the lead investigators and sponsor representatives) after the first 6 subjects had completed 12 weeks treatment as outlined above. This might result in reduced dosing frequency if there were safety concerns or poor tolerability. Overall, the safety profile was concluded to be acceptable and the committee endorsed continuation of the trial using the same dose, and extension of the treatment duration to 48 weeks. Recruitment beyond the 6 first subjects was not stopped during the review period. If needed, unscheduled visits will be conducted at investigator's discretion.

The trial will be conducted in compliance with the protocol, all applicable regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

Overall, there is a good chance for study subjects to gain improvement from their condition through participation in the study and the study will, if successful, be an important step on the path to an approved treatment for pulmonary NTM infection.

7. TRIAL OBJECTIVES AND PURPOSE

7.1. Primary Objective

The primary objective is:

- To investigate efficacy of inhaled molgramostim on NTM sputum culture conversion to negative.

7.2. Secondary Objectives

The secondary objectives are:

- To investigate efficacy of inhaled molgramostim on NTM sputum smear conversion to negative.
- To investigate efficacy of inhaled molgramostim on reduction of NTM bacterial load in sputum.
- To investigate efficacy of inhaled molgramostim on exercise capacity.
- To investigate efficacy of inhaled molgramostim on Patient Reported Outcomes.
- To investigate safety of inhaled molgramostim in subjects with NTM infection.

7.3. Endpoints

7.3.1. Efficacy Endpoints

7.3.1.1. Primary Efficacy Endpoint:

- Sputum culture conversion defined as at least three consecutive negative sputum samples during the treatment period.

7.3.1.2. Secondary Efficacy Endpoints:

- Sputum smear conversion defined as at least three consecutive negative AFB stained sputum smears on microscopy during the treatment period in subjects who were smear positive at Baseline.
- Durability of sputum culture conversion (defined as conversion at or before Week 48 and culture still negative at 12-weeks follow-up).
- Durability of sputum smear conversion (defined as conversion at or before Week 48 and smear still negative at 12-weeks follow-up).
- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.
- Change in semi-quantitative grade of sputum cultures from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.

- Change in symptom scores (assessed using Lower Respiratory Tract Infections – Visual Analogue Scale (LRTI-VAS) and Quality of Life Questionnaire– Bronchiectasis (QOL-B) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in Global Rating of Health (GRH) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in body weight from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in 6MWD, oxygen desaturation and Borg CR10 scores during a 6MWT from Baseline to Week 12, 24, 48 and 12-week follow-up.

7.3.2. Safety Endpoints

- Number of AEs, SAEs, ADRs, severe AEs and AEs leading to treatment discontinuation during the trial period.
- Change in WBC and differentials in blood from Baseline to Weeks 4, 12 24, 32, 40, 48 and 12-week follow-up.
- Change in DLCO from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and at 12-week follow-up.
- Change in forced expiratory volume in 1 second (FEV_1) (% predicted) and forced vital capacity (FVC) (% predicted) from Baseline to Weeks 12, 24, 32, 40 and 48.
- Development of anti GM-CSF antibodies at Week 4, 12, 24, 32, 48 and at 12-week follow-up.

8. INVESTIGATIONAL PLAN

8.1. Overall Trial Design

This is an open-label, non-controlled, multicenter, pilot clinical trial of inhaled molgramostim in subjects with persistent pulmonary NTM infection.

The primary objective is to investigate efficacy of inhaled molgramostim on NTM sputum culture conversion to negative. The primary endpoint is sputum culture conversion defined as at least three consecutive negative sputum samples during the treatment period.

Secondary objectives are to investigate the efficacy of inhaled molgramostim on NTM sputum smear conversion to negative, on reduction of NTM bacterial load in sputum and on Patient Reported Outcomes, exercise capacity as well as evaluation of the safety of inhaled molgramostim in these subjects.

Secondary efficacy endpoints and the safety endpoints are detailed in Section 7.3.

The study will comprise a Screening Visit, Baseline Visit, a 48-week treatment period and a 12-week follow up period. The Screening Visit (Visit 1) will be conducted up to 10 weeks prior to the Baseline Visit (Visit 2) to determine eligibility. Adult subjects with a history of chronic NTM infection with at least 2 positive cultures in the prior two years, of which at least one is within the last 6 months prior to Screening, will be considered for enrollment. Subjects should provide a positive NTM sputum culture at Screening to be eligible.

Two subgroups of subjects will be recruited:

- Group 1: Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit.
- Group 2: Subjects who remain sputum culture positive but have either stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or never started such treatment.

The study will include 30 subjects.

The treatment period will consist of 14 trial visits (Screening, Baseline, and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48; Visits 1-14) and a follow-up visit (Visit 15) 12 weeks after end of treatment. The visits at Weeks 28, 36 and 44 (Visits 9, 11 and 13) will include a telephone contact, all other visits will include a clinic visit.

At the Baseline Visit (Visit 2), eligible subjects will start treatment with inhaled molgramostim administered via the PARI eFlow nebulizer.

At each visit (Visits 1-15), sputum samples for staining and microscopy, and microbiological culture will be collected. If required, induced sputum may be obtained according to local standards. On the days of clinic visits (Visits 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15), subjects will be asked to collect two additional sputum samples at home, preferably on the consecutive days after the site visit. On the days of the telephone contact visits (Visits 9, 11 and 13), three sputum samples will be collected at home, preferably on consecutive days.

Any AEs will also be collected at Baseline and all subsequent visits (Visits 2-15), At all clinic visits a pregnancy test/contraceptive check will be conducted, changes in concomitant medication, measurement of body weight and an assessment of DLCO will be performed. A computed tomography (CT) scan will be conducted at Baseline (Visit 2) if not performed within 6 months prior to Baseline. If DLCO drops by at least 20% at two consecutive visits the CT scan may be repeated. A CT scan can be performed after 48 weeks of treatment if this is a part of the local routine clinical practice.

A physical examination and an electrocardiogram (ECG) will be performed at Screening and Weeks 24 and 48 (Visits 1, 8 and 14) and vital signs will be collected at Screening, Baseline, and Weeks 4, 12 24, 32, 40 and 48 (Visits 1, 2, 3, 5, 8, 10, 12 and 14). Spirometry will be conducted at Baseline and at Weeks 12, 24, 32, 40 and 48 (Visits 2, 5, 8, 10, 12 and 14). A 6MWT will be conducted at Baseline, at Weeks 12, 24 and 48 and at the 12-week follow-up visit (Visits 2, 5, 8, 14 and 15). Blood samples for safety laboratory testing will be taken at Screening, Baseline, and at Weeks 4, 12, 24, 32, 40, 48 and at the 12-week follow-up visit (Visits 1, 2, 3, 5, 8, 10, 12, 14, 15). Anti-GM-CSF will be assessed at Baseline, at Week 4, 12, 24, 32, 48 and at the 12-week follow-up visit (Visits 2, 3, 5, 8, 10, 14 and 15). Patient reported outcomes (QoL-B, LRTI-VAS and GRH) will be assessed at Baseline and at all post Baseline clinic visits (Visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15). For subjects having a chest X-ray during the study period as part of the routine local clinical practice, the results from the X-ray will be recorded.

Participating subjects will be encouraged to contact the clinic between visits if they experience adverse events (AEs), worsening of their condition or have any other concerns. If needed, unscheduled visits will be conducted at investigator's discretion.

A schedule of study assessments is available in Table 1 .

Treatment with inhaled molgramostim will be given at a dosage of 300 µg once daily for 48 weeks. All subjects in the trial initially consented to 24 weeks of treatment. All enrolled subjects continuing with 48 weeks of treatment will re-consent and follow the visits schedule as described above.

Subjects that do not wish to continue to 48 weeks of treatment will end treatment after 24 weeks (visit 8) and will attend the follow-up visit 12-weeks later as per the visit schedule outlined in Protocol Version 2.0 or 3.0.

Subjects who complete the initial 24-week treatment period prior to the approval of Protocol Version 4.0 will proceed to the 12 week follow up as per the visit schedule in Protocol Version 2.0 or 3.0. Once Protocol Version 4.0 is approved they will be asked to re consent and re-initiate treatment. This will occur at the next trial visit or at an unscheduled visit. These subjects will not receive the whole 48-week treatment. The will receive treatment for an additional 24 weeks minus the number of weeks that they have been in follow up.

Subjects that do not wish to re consent and re initiate treatment will stay in follow up and attend the follow-up visit as per the visit schedule outlined in Protocol Version 2.0 or 3.0.

At Baseline and at Weeks 4, 12, 24, 32 and 40 (Visits 2, 3, 5, 8, 10 and 12), dosing will take place in the clinic after blood sampling. A data review was conducted after the first 6 subjects had completed 12 weeks of treatment. If safety concerns or poor tolerability were identified in this review, the review committee might decide on less frequent dosing for subsequent subjects

in the study. The review was conducted on 16 September 2018 and concluded that there were no safety issues of significant concern and the dose was unchanged. In order to obtain more robust treatment responses it was decided to extend the treatment duration from 24 to 48 weeks. Any changes to the conduct of the study such as change of dose, dose regimen or duration will be documented in a protocol amendment.

During the study, subjects in Group 1 will continue use of antimycobacterial treatment. All changes in antimycobacterial treatment will be recorded, including reasons for each change. In case of worsening of NTM pulmonary disease, antimycobacterial treatment may be added or a dosage increase of antimycobacterial treatment may be applied as rescue treatment, according to investigator's discretion.

8.1.1. Trial Period

Estimated date first subject screened: Q1 2018

Estimated date last subject completed (24 weeks treatment period): Q4 2019

Estimated date last subject completed (follow-up period): Q1 2020

The duration of trial participation for each subject is approximately 60 to 70 weeks:

- Screening period for the subjects is up to 10 weeks
- Treatment period up to 48 weeks (+/- 7 days)
- Follow-up for 12 weeks (+/- 7 days)

8.1.2. End of Trial

The end of the trial is defined as the last subject's last visit (LSLV).

8.1.3. Trial completion

Trial completion is defined as the date of the Clinical Trial Report (CTR).

8.2. Number of Subjects

It is planned that 30 subjects will be enrolled. No formal sample size calculation was done as this is an initial pilot study.

8.3. Treatment Assignment

At Screening (Visit 1), the subject will be assigned a site-specific subject number that will continue to be the unique identifier throughout the trial. The subject number will be generated automatically by the electronic data capture system used in the trial. The subject number will be in the following format XX-YYY. The letter XX is the site number and YYY the consecutive subject number starting at 101 at each site.

At the Baseline visit, all subjects found to be eligible according to the inclusion/exclusion criteria will be classified into the following treatment groups by a central electronic data capture system:

- Group 1: Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit.
- Group 2: Subjects who remain sputum culture positive but have either stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or never started such treatment.

Patients successfully assigned to a subgroup will then start treatment with open-label molgramostim nebulizer solution.

8.4. Dose Adjustment Criteria

A data review was conducted by a safety review committee comprised of the lead investigators and sponsor representatives after the first 6 subjects had completed 12 weeks of treatment. If safety concerns or poor tolerability were identified in this review, the review committee might decide on less frequent dosing for subsequent subjects in the study. The review concluded that no dose adjustment was required. Any changes to the conduct of the study such as change of dose regimen will be documented in a protocol amendment.

Subjects who experience poor tolerability to treatment (i.e. unacceptable respiratory or gastrointestinal symptoms, the nature of which may be assumed to be reversible) may reduce the dose. Prior to dose reduction, the Sponsor medical monitor must be consulted.

8.4.1. Safety Criteria for Adjustment or Stopping Doses

No prespecified safety criteria have been defined for the safety review committee.

8.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

8.5. Criteria for Study Termination

The investigator or the sponsor may terminate this trial prematurely for any reasonable cause. The Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and Competent Authorities (CAs) should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects in the trial, or potential trial subjects
- A decision on the part of the sponsor to suspend or discontinue development of the IMP

If the CA obtains information that raises doubts about the safety or scientific validity of the clinical trial, the CA can suspend or prohibit the trial. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week (Directive 2001/20/EC, Article 12, Section 1).

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects and should assure appropriate therapy and follow-up for the subjects.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

Subject fulfilling all inclusion and none of the exclusion criteria can be enrolled in the trial. An enrolled subject is defined as a subject receiving treatment with the trial IMP.

9.1. Subject Inclusion Criteria

1. History of chronic pulmonary infection with MAC or *M. abscessus* (defined as at least 2 documented positive sputum cultures in the prior 2 years, of which at least one was obtained in the 6 months prior to Screening).
2. Subject fulfills one of the following criteria:
    - Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit
    - Subjects who remain sputum culture positive but have either stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or never started such treatment.
3. Ability to produce at least 2 mL of sputum or be willing to undergo an induction that produces at least 2 mL of sputum for clinical evaluation.
4. Female or male ≥18 years of age.
5. Females who have been post-menopausal for more than 1 year or females of childbearing potential after a confirmed menstrual period using a highly efficient method of contraception (i.e. a method with less than 1% failure rate such as combined hormonal contraception, progesterone-only hormonal contraception, intrauterine device, intrauterine hormone- releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence[1]), during and until thirty (30) days after last dose of trial treatment. Females of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at dosing at Baseline (Visit 2) and must not be lactating.
6. Males agreeing to use condoms during and until thirty (30) days after last dose of medication, or males having a female partner who is using adequate contraception as described above.
7. Willing and able to provide signed informed consent.

[1] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures specified in the protocol as judged by the investigator

9.2. Subject Exclusion Criteria

1. Subjects diagnosed with cystic fibrosis.
2. Prior therapy with inhaled or systemic GM-CSF.
3. Subjects with hemoptysis of ≥60 mL in a 24 hour period within 4 weeks prior to Screening.
4. Concurrent disease with a life expectancy of less than 6 months.
5. History of, or present, myeloproliferative disease, leukemia or other hematological malignancy.
6. Active pulmonary malignancy (primary or metastatic); or any malignancy requiring chemotherapy or radiation therapy within one year prior to Screening or anticipated during the study period.
7. Active allergic bronchopulmonary mycosis or connective tissue disease, inflammatory bowel disease or other autoimmune disorder requiring therapy associated with significant immunosuppression, such as systemic corticosteroids at a dose equivalent of 10 mg/day or more of prednisolone, within 3 months prior to Screening or anticipated during the study period.
8. Pulmonary tuberculosis requiring treatment or treated within 2 years prior to Screening.
9. HIV infection or other disease associated with significant immunodeficiency.
10. History of lung transplantation.
11. Any change in chronic NTM multi-drug antimycobacterial regimen within 28 days prior to Screening.
12. Treatment with any investigational medicinal product within 3 months of Screening.
13. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product
14. Any other serious medical condition which in the opinion of the investigator would make the subject unsuitable for the trial.

9.3. Subject Withdrawal Criteria

9.3.1. Discontinuation from Trial Treatment

Subjects may be discontinued from treatment and assessments at any time, if deemed necessary by the investigator.

Potential reasons for discontinuation of treatment are:

- Lack of efficacy/worsening of disease
- Unacceptable AE
- Serious hypersensitivity reaction
- Pregnancy

Those who discontinue treatment will not automatically be withdrawn from the trial but will be encouraged to continue to follow the same visit schedule. For example: if treatment is discontinued at Week 4 (Visit 3) the subject will be encouraged to attend the remaining visits.

The reason and date the subject is discontinued from treatment will be documented in the electronic case report form (eCRF).

9.3.2. Withdrawal from the Trial

Subjects are free to discontinue their participation in the trial at any time. Withdrawal from the trial will not affect or prejudice the subject's further care or treatment. Potential reasons for withdrawal of subjects from the trial are:

- Screening failure
- The decision of a subject to withdraw from the trial (including if the subject withdraws informed consent)
- Unacceptable treatment response
- Unacceptable adverse event
- Subject is lost to Follow-up
- Other reason(s) (e,g incorrect enrollment)

The reason and date the subject is withdrawn from the trial will be documented in the eCRF (e.g. lost to follow-up, consent withdrawn, incorrect enrolment, AEs, etc.). If a subject is withdrawn from the trial, the investigator should attempt to complete all required trial assessments (such as those at Week 48 if withdrawn during the treatment period).

All AEs should be followed-up according to Section 12.15.

If a subject is withdrawn from the trial, all data collected until the time of withdrawal will be used in the data presentations unless consent to use the data was withdrawn by the subject.

10. TREATMENT OF SUBJECTS

10.1. Description of Study Drug

Table 3: Investigational Product

	Investigational Product
Product Name:	Molgramostim nebulizer solution
Dosage Form:	Nebulizer solution
Unit Dose	300 µg
Route of Administration	Inhalation using the PARI eFlow nebulizer (PARI Pharma GmbH)
Physical Description	Clear, colourless solution containing molgramostim, a recombinant human Granulocyte Macrophage Colony Stimulating Factor (rhGM-CSF). Excipients are mannitol, polyethylene glycol 4000, Recombumin® Prime, disodium phosphate (anhydrous), citric acid (monohydrate), and water for injection

10.2. Prohibited Medications

The following **prior medications are not allowed** (See exclusion criteria Section 9.2):

- Treatment with inhaled or systemic GM-CSF
- Therapy associated with significant immunosuppression such as systemic prednisolone at a dose equivalent of 10 mg/day or more within 3 months prior to Screening

10.3. Treatment Compliance

Subject compliance in the treatment period will be evaluated by unused and used vial counts. Subjects will be asked to return all unused and empty vials at the next clinic visit. Vials will be visually inspected for opening. The number of unused and empty vials will be counted upon return and recorded in the drug accountability log kept at the site.

10.4. Randomization and Blinding

Not applicable.

10.5. Subject Identification List

The investigator will maintain a list of all subjects screened in the trial at the site. This list includes each subject's identity, date of enrolment and corresponding subject number so that any subject may be identified if required for any reason.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

Each vial of molgramostim contains 300 µg molgramostim in 1.2 mL solution (250 µg/mL).

11.2. Study Drug Packaging and Labeling

All manufacturing and packaging will be performed in accordance with current Good Manufacturing Practice (GMP).

Individual medication kits containing trial medication for four weeks will be supplied in adequate amounts at the dispensing visits.

Labels will comply with local regulations and will be printed in local language.

11.3. Study Drug Storage

The IMP must be stored at 2-8°C.

The IMP will be stored at the trial site or the at the site pharmacy as required by local regulations and laws for the participating sites. The Investigator will ensure that the IMP will be stored in appropriate conditions in a secure location with controlled access. The storage compartment must be monitored and the temperature documented. Any deviations in storage temperature must be reported to sponsor without delay. In case of a temperature deviation, the IMP must not be used until acceptance from the sponsor.

The IMP kits will be dispensed to the subject at Baseline (Visit 2), and at Weeks 4, 8, 12, 16, 20, 24, 32 and 40 (Visits 3, 4, 5, 6, 7, 8, 10 and 12) during the treatment period.

Subjects will be instructed to store the kit at 2-8°C in a safe and secure place out of the reach of children. The IMP should not be frozen or shaken and not be used beyond the expiration date on the vial.

Subjects will be asked to return used and unused medication at the next clinic visit to check compliance.

11.4. Study Drug Preparation

Not applicable.

11.5. Administration

The PARI eFlow nebulizer system (PARI Pharma GmbH, Germany) will be used to administer the IMP. The eFlow Nebulizer Handset is a single subject use, reusable electronic nebulizer. It includes a fine particle aerosol generator (perforated vibrating membrane) defined by a 30L mesh and an aerosol chamber that can produce aerosols with high density of active drug, precisely defined droplet size and a high proportion of respirable droplets.

All subjects, investigators and trial nurses will be trained in IMP administration and medical device maintenance procedure. The training of the subjects will be arranged prior to

administration of the subject's first dose of IMP and checked in clinic on first dosing. The subject will also receive written instructions.

The subject will administer the first dose of IMP at the Baseline visit (Visit 2) under the supervision of trial personnel.

During the treatment period at Weeks 4, 12, 24, 32 and 40 (Visits 3, 5, 8, 10 and 12), subjects will be asked not to take their study treatment prior to the clinic visit because blood samples for laboratory testing will be taken. At these visits dosing will take place in the clinic after the blood samples have been taken. The subject should be instructed to take the last dose the day before the 48-week visit (Visit 14).

11.6. Study Drug Accountability

It is the responsibility of the investigator or trained designee to determine investigational drug accountability and complete the drug accountability log. Drug accountability will be reviewed by the monitor during monitoring visits and at the completion of the trial.

Copies of all Drug Receipt Confirmations, Returned Clinical Supplies Reconciliation Forms and Drug Accountability Logs will be retained in the trial file. These forms are subject to regulatory inspection at any time.

11.7. Study Drug Handling and Disposal

Unused IMP must be returned to supply vendor, or sent for destruction after agreement with the Sponsor, but only after the trial and overall drug accountability has been completed. A list of trial drug, used, or returned must be prepared and signed by the investigator or designee; an account must be given for any discrepancies.

12. ASSESSMENTS

The timing of all trial assessments is shown in the Schedule of Procedures in Table 1.

12.1. Informed consent

All subjects must provide informed consent in accordance with the origins of the Declaration of Helsinki and the applicable laws of the country. The written informed consent must be obtained before any trial activities are performed, incl. any period for wash-out of concomitant medication.

It is the responsibility of the principal investigator or a sub-investigator to obtain the written informed consent from the subject.

The investigator must explain the nature of the trial, its purpose, the assessments involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail and provide the subject with a copy of the information sheet and the consent form. Information to a subject can be delegated to a nurse, but the investigator must be available for questions and both the nurse and the investigator must sign the consent form to document this.

The subject must be given sufficient time to consider the trial before deciding whether to participate. Each subject must be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject must sign and date the informed consent form before he/she enters the trial (i.e. before any trial related activity). The investigator must give a copy of the signed informed consent to the subject. The investigator should keep the original.

If information becomes available that may be relevant to the subject's willingness to continued participation in the trial the subject information sheet will be updated by Savara and approved by an IEC/IRB and the Competent authorities. The subject must be informed in a timely manner about the updated subject information sheet and written informed consent must be obtained.

12.2. Collection of Sputum Samples for Microbiological Characterization and Quantification

Sputum samples for staining and microscopy, and microbiological culture will be collected at the timepoints shown in in Table 1.

The analysis of the samples will be performed at a specialized mycobacterial laboratory.

If required, induced sputum may be obtained using local standards.

On the days of clinic visits (Visits 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15), subjects will be asked to collect two additional sputum samples at home, preferably on the consecutive days after the site visit. On the days of the telephone contact visits (Visits 9, 11 and 13), three sputum samples will be collected at home, preferably on consecutive days.

The sputum samples must be refrigerated immediately after sampling. Details regarding the collection and handling of sputum samples will be provided in a separate document.

AFB staining (fluorescence and /or ZN stain) will be used to identify NTM in sputum and conduct a semi-quantitative assessment of bacterial load (graded as 0, occasional, 1+, 2+, 3+). Smears will also be fixated on slides and all slides will be submitted to a central laboratory for a second assessment.

Microbiological culture to identify growth of NTM will be conducted using established standards. A semi-quantitative assessment of sputum cultures will be performed. Identification to NTM species level will be conducted on positive samples using established methods.

If sufficient sputum volume is obtained, an additional aliquot will be frozen and stored for potential post-hoc analysis by quantitative polymerase chain reaction (PCR). Such PCR analysis will be performed no later than two years after trial completion. PCR data will not be included in the CTR, but reported separately.

Routine bacteriology and fungal culture will be performed.

12.3. Prior and Concomitant Medication

The subject's use of all concomitant medication must be recorded in the eCRF.

All relevant prior medication should also be recorded. This includes the most recent course of antimycobacterial treatment taken within 3 years prior to the screening visit. Other prior medication should also be recorded if considered relevant by the investigator. Standard information about the medication will be collected including the name of medication, dose, frequency, administration route and treatment period.

Changes to medication not provided as a part of this trial should be kept to a minimum during the trial. However, if considered necessary for the subject's well-being concomitant medication may be given at the discretion of the investigator according to local standard care. All changes will be recorded, including reasons for each change.

In case of worsening of NTM pulmonary disease, antimycobacterial treatment may be added or a dosage increase of antimycobacterial treatment may be applied as rescue treatment, according to investigator's discretion.

At each visit the investigator should ask the subject about use of concomitant medication. All concomitant medication must be documented in the subject's medication records and in the eCRF. Furthermore, each change in concomitant medication (e.g. new treatment, discontinuation of treatment and change in dosage/routine) during the trial must be documented in the same way.

12.4. 6-Minute Walk Test (6MWT)

Exercise capacity will be assessed using the 6MWT at the timepoints shown in Table 1.

The 6MWT will be performed in accordance with European Respiratory Society/American Thoracic Society (ERS/ATS) guidance [Holland 2014] by technicians with documented training and experience of performing the 6MWT in accordance with the referred ERS/ATS guidance. The 6MWT should be performed twice at each visit in accordance with the ERS/ATS guidelines.

Data from both tests should be entered in the eCRF. Parameters to be recorded comprise pre and post walk dyspnea score using the Borg (CR-10) Dyspnea Score, blood oxygen saturation (SpO_2)

(%) at start, worst SpO_2 (%) during the walk, distance walked (6MWD; m), duration of the walk (minutes and seconds), O_2 flow rate if applicable, reason for stopping early (if applicable).

Trial specific instructions will be provided in a separate document.

If a subject is on long-term oxygen therapy, oxygen should be given at their standard flow rate and held constant throughout the test. The tests conducted after Baseline should be performed using the same oxygen conditions that were used at Baseline.

12.5. Patient Reported Outcomes

The following patient reported outcomes will be assessed at the timepoints shown in Table 1.

A sample of all questionnaires are presented in Appendix 4 .

- Clinical symptoms will be assessed using Lower Respiratory Tract Infections – Visual Analogue Score (LRTI-VAS),
- Quality of Life Questionnaire– Bronchiectasis (QOL-B),
- Global Rating of Health (GRH).

12.5.1. Lower Respiratory Tract Infections – Visual Analogue Score

For each of the clinical symptoms of lower respiratory tract infections (dyspnea, fatigue, cough, pain, and sputum) the subject will assess the severity using a 10cm visual analogue scale ranging from 0=no symptoms to 10 =worst possible symptoms. The results from visual analogue scores will be entered in the eCRF.

12.5.2. Quality of Life Questionnaire– Bronchiectasis (QOL-B)

The QOL-B questionnaire in the local language will be used to assess subject's quality of life. The results from QOL-B will be entered in the eCRF.

12.5.3. Global Rating of Health (GRH)

Global Rating of Health will be assessed as an interviewer questionnaire. Global Rating of Health assesses global health as "excellent, good, fair or poor". The results from GRH will be entered in the eCRF

12.6. Subject Diary

The subject will receive a subject diary at the timepoints shown in Table 1. The subject diary will include information about the IMP, the use of the nebulizer and home collection of sputum samples. The subject will be asked to record AEs experienced between the visits in the subject diary. The subject will also be asked to place the tear-off label from the IMP box in the subject diary.

12.7. Adverse Events

Any AEs will be reported at every visit from Baseline (Visit 2) to the completion of the 12-week follow-up (Visit 15). Subjects will be encouraged to contact the clinic in between visits if they

experience AEs or have any concerns. For further information of definitions and reporting of AEs and SAEs, see Section 12.15.

12.8. Demographic/Medical History/Body Measurements

The following demographic and body measurement data and medical history will be collected at the timepoints shown in Table 1.

- Date of birth
- Weight (kg) in indoor clothes
- Height (cm) without shoes
- Sex
- Race (White/Asian/Black/American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander)
- Smoking (Previous/Current/Never)
- Relevant prior and concurrent disorders
- Prior and current NTM infections including dates and species

12.9. Physical Examination

All subjects will undergo a standard physical examination at the timepoints shown in Table 1.

Complete physical examinations will include at a minimum a review of the subject's general appearance, head, eyes, ears, nose, and throat (HEENT), neck, heart, lungs, abdomen, extremities, skin, and general neurological system. Any abnormalities will be recorded in the eCRF and assessed as 'clinically significant' or 'not clinically significant'.

Symptom-oriented or brief physical examinations may be performed as clinically indicated. New abnormal clinically significant physical examination findings not present during the baseline visits should be recorded as AEs and followed during subsequent visits.

12.10. Vital Signs

The following vital signs will be assessed at the timepoints shown in Table 1.

- Resting systolic and diastolic blood pressure (mmHg), after 5 minutes sitting
- Resting heart rate (beats per minute), after 5 minutes sitting
- Resting respiration rate (breaths per minute), after 5 minutes sitting
- Oral body temperature (°C)

The observed values will be recorded and assessed as 'normal' or 'abnormal'. Abnormal findings will be assessed as 'clinically significant' or 'not clinically significant'.

12.11. Electrocardiogram (ECG)

A 12-lead ECG will be assessed using a standard ECG machine according to local procedures at the time points shown in Table 1.

No central overreading will be performed.

Heart rate, QRS, PR and QT intervals will be recorded from the ECGs. The ECGs will be interpreted and signed and dated by the investigator or his/her designee. Results will be classified as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. All clinically significant abnormalities will be recorded as AEs.

12.12. Radiology

12.12.1. CT Scan

If not performed within 6 months prior to Baseline, a CT scan will be performed at the Baseline visit (Visit 2). If there is a decrease in DLCO of at least 20% at two consecutive visits the CT scan may be repeated and the results recorded.

12.12.2. Chest X ray (only if conducted as part of the local routine clinical practice)

Chest X-rays are not required for the study but if subjects have a chest X-ray as part of the local routine clinical practice during the study period, the reason and the results from the chest X-ray will be recorded as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. Clinically significant abnormalities that were not present before the study or that worsened during the study (based on medical records) will be recorded as AEs.

12.13. Pulmonary Function Tests

12.13.1. DLCO

DLCO will be done using local appropriately calibrated equipment by site staff with documented training in lung function testing at the time points shown in Table 1.

The DLCO measurements should be performed in accordance ATS/ERS guidelines [Graham 2017]. Parameters to be recorded are DLCO (absolute measured) and DLCO (predicted). The average of two valid tests will be calculated.

12.13.2. Spirometry

FEV_1 and FVC will be assessed using a local appropriately calibrated spirometer by site staff with documented training in lung function tests at the time points shown in Table 1.

The FEV_1 and FVC are measured as 3 valid measurements and the highest value will be entered in the eCRF.

12.14. Laboratory Assessments

Blood samples for laboratory assessment will be taken at the timepoints shown in Table 1.

The total amount of blood required for sampling is approximately 240 mL with a maximum of 30 mL for one visit.

All blood samples should be taken **prior to dosing** at the clinic visit.

12.14.1. Levels of Anti-GM-CSF Antibodies

Analyses for anti-GM-CSF antibodies will be performed at a central laboratory.

12.14.2. Laboratory Safety Assessments

The laboratory safety analyses (hematology, clinical chemistry and urinalysis) will be performed by a central laboratory at the timepoints shown in Table 1.

Sampling methods and procedures will be in accordance with local routine care. A trial specific laboratory manual for sampling, handling, storage and shipment of samples will be provided to the site personnel. The manual will be provided to the site before start of the trial.

The observed values will be recorded and assessed as 'normal' or 'abnormal'. Abnormal findings will be assessed as 'clinically significant' or 'not clinically significant'.

12.14.2.1. Blood Hematology

The following parameters will be analyzed:

Hemoglobin, Red Blood Cell Count (RBC), Red Blood Cell Distribution Width (RDW), Hematocrit (PCV/EVF), Mean cell volume (MCV), Mean cell hemoglobin (MCH), Mean cell hemoglobin concentration (MCHC), Platelet count, White cell count, and white cell differential absolute count: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, and Prothrombin Time International Normalized Ratio (PT-INR)

12.14.2.2. Blood Chemistry

The following parameters will be analyzed:

Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyl Transpeptidase (GGT), Alkaline Phosphatase, Bilirubin, Urea, S-Creatinine, estimated glomerular filtration rate (eGFR), Potassium, Sodium, Calcium, Chloride, Phosphate, Total protein, Albumin, Lactate dehydrogenase (LDH), C-Reactive Protein (CRP), and Glucose (non-fasting)

12.14.2.3. Urinalysis

The following parameters will be analyzed:

pH, Glucose, RBCs, WBCs, Protein, and Microalbuminuria.

12.14.2.4. Pregnancy Screen

A serum pregnancy test and contraceptive check will be performed for female subjects at the timepoint shown in Table 1. A urine pregnancy test will also be performed before dosing at Baseline (Visit 2) in order to immediately confirm that the subject is not pregnant.

12.15. Adverse and Serious Adverse Events

12.15.1. Definition of Adverse Events

12.15.1.1. Adverse Event (AE)

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.

An AE can therefore be any unfavorable 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.

12.15.1.2. Serious Adverse Event (SAE)

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- May jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above (Important Medical Events)

Life-threatening in the definition of a SAE or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

For important medical events, medical judgement should be exercised in deciding whether an AE/reaction is serious.

The severity of an adverse reaction is largely determined by the outcome of the medical occurrence. An adverse reaction should only be termed "serious" if hospitalization did in fact take place as a result of it. As a rule, hospitalization is the admission to a hospital with at least one overnight stay.

The presentation of a patient in the emergency room (casualty center, health care center) alone without subsequent in-patient admission does not yet fulfill the criterion hospitalization. However, it should be confirmed whether any of the other criteria mentioned above justifies an adverse reaction being classified as "serious" or at least "medically significant.

If the Investigator becomes aware of an SAE with a reasonable relationship to the IMP after the subject has left the trial, this SAE must also be reported (post-trial event).

12.15.1.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an AE which

- has a reasonable possibility of causal relationship to an IMP,

- is serious; and
- is unexpected

Therefore, due to the nature and/or severity of the adverse reaction, a SUSAR is not consistent with the applicable product information (i.e. the reference safety information in the IB) for the IMP used in this study.

12.16. Recording Adverse Events

All trial subjects will be carefully monitored for the occurrence of AEs during the trial period from Baseline (Visit 2) to the 12-week follow-up visit (Visit 15). The investigator will collect AEs using a non-leading question such as “have you experienced any new health problems or worsening of existing conditions” as well as reporting events directly observed or spontaneously volunteered by subjects.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the subject, or reported in answer to an open question by the investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding trial drug
- Opinion on causality
- Seriousness
- Outcome

Severity

Severity describes the intensity of an event, and will be assessed as:

Mild

The AE is easily tolerated and does not interfere with daily activity.

Moderate

The AE interferes with daily activity, but the subject is still able to function. Medical intervention may be considered.

Severe

The AE is incapacitating and requires medical intervention.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description.

Causality

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE.

Causality will be assessed as:

Probable

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IMP, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IMP, but which could also be explained by concurrent disease or other drugs or chemicals. Information on IMP withdrawal may be lacking or unclear.

Unlikely

A clinical event, including laboratory test abnormality, with a temporal relationship to IMP administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Not applicable

This assessment can be used e.g. in cases where the subject did not receive any treatment with IMP or if the causality cannot be judged because information is insufficient or contradictory.

Outcome

The outcome of AEs has to be described by following criteria:

- Recovered
- Not Recovered
- Recovered with sequelae
- Fatal
- Unknown.

Follow-up of Subjects after Adverse Events

Any AE that is ongoing when the subject is withdrawn from the trial should be followed-up until the AE is resolved or the investigator decides that the AE is stable and needs no further Follow-up.

Abnormal Laboratory Values/Vital Signs

An asymptomatic abnormal laboratory/vital sign finding should only be reported as an AE if it is clinically significant according to the investigator's assessment, if it fulfils the criteria for an SAE or if it causes the subject to discontinue the trial.

If an abnormal laboratory/vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory/vital sign result should be considered additional information.

12.17. Reporting Adverse Events

12.17.1. Reporting of Serious Adverse Events

The investigator is responsible for ensuring that all SAEs are reported to the sponsor immediately, using a study-specific SAE form, but in any event no later than 24 hours of any site staff becoming aware of the event from the time the informed consent has been signed, up to the last visit. Reporting of SAEs will also be described in a trial-specific procedure.

After that period of time only serious adverse reactions (events related to study medication) have to be reported. SAEs occurring to a patient after the patient has completed the clinical trial and for which a reasonable possibility of a causal relationship is assessed by the Investigator, must be reported by the Investigator to Premier Research regardless of the time that has elapsed (post-trial events). The SAE form has to be completed in English.

Initial reports should be followed as soon as possible by detailed written reports. The initial and Follow-up reports should identify subjects by unique code numbers assigned in the trial. The subjects' names, personal identification numbers, and/or addresses must not be included. The following information is mandatory for the initial report:

- Subject trial ID
- Trial treatment (blinded, if applicable)
- Start date (time, if relevant) of the trial treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the investigator should supply the sponsor and the IEC (if applicable) with any additional requested information (e.g. autopsy reports and terminal medical reports).

The Investigator must contact Premier Research by email or fax directly to Premier Research Pharmacovigilance and Device Safety in case of all serious adverse events (SAEs) **within 24 hours after awareness** of the event.

SAE REPORTING CONTACT DETAILS

Company: Premier Research

Department: Pharmacovigilance and Device Safety (PVDS)

E-mail: SavaraSafety@premier-research.com

Fax: +421 2 68203713

Note: If there is local legislation requiring investigators to report AEs to the CA or the IEC, the investigator should also comply with this legislation. If any such reporting is planned, this must be stated in the SAE report, and once the reporting has been performed, a copy of the reporting documentation must be enclosed with the Follow-up SAE report to the sponsor.

The initial SAE report should be completed by the investigator immediately, even if not all data are available. Relevant follow-up information must be faxed or sent by e-mail to Premier PV as soon as possible. SAE-Follow-Up reports also have to be recorded on the study specific SAE form. A follow-up report should be clearly marked as such and linked to the initial report.

The medical term of the SAE should be an event, reaction or diagnosis rather than a list of symptoms. It is important to enter the most appropriate event term in the corresponding field.

The Investigator should complete all the details requested including dates of onset, severity, corrective therapies given, outcome and his opinion as to whether the reported event is possibly drug-related.

In the case of death of a trial patient, the Investigator has to provide any additional information necessary as requested by the sponsor, the competent authorities concerned and ethics committees concerned.

12.17.2. SUSAR Reporting Procedure

According to national legislation and European directives and guidelines, the sponsor of the clinical trial will report all SUSARs to the CA and Ethics Committee in all Member States concerned, to the European clinical trials database (Eudravigilance Clinical Trial Module - EVTCM), and if applicable, to other regulatory authorities according to local laws and regulations.

The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to Ethics Committee (if required by local regulations), and in any case no later than seven (7) days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

Any other SUSARs shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

The investigator should be aware of local reporting regulations to the Ethics Committee/Institutional Review Board (IRB). The Sponsor will either supply the investigator with the reports which should be passed on to the Ethics Committee/IRB or report directly to the Ethics Committee/IRB depending on local regulations.

12.17.3. Adverse Events of Special Interest

There are currently no AEs of special interest identified due to limited previous experience of Savara's molgramostim.

12.17.4. Precautions/Overdose

No acute systemic or hypersensitivity reactions have been reported in subjects receiving inhaled sargramostim or molgramostim products.

There is no known antidote to molgramostim. In the event of overdose, symptomatic management is indicated.

Based on information from similar products, overdose may manifest with respiratory symptoms, e.g. bronchospasm, wheezing, dyspnea, decreased pulmonary function or cough.

Hematologic findings such as leukocytosis, eosinophilia and neutrophilia may occur in case of systemic exposure. With high systemic doses of similar products, the following symptoms have been observed: tachycardia, hypotension, dyspnea, and flu-like symptoms. These symptoms abated quickly on symptomatic treatment. More information is available in the IB.

12.17.5. Pregnancy

Female subjects will be instructed to notify the investigator immediately if they become pregnant during the trial. Male subjects will be instructed to notify the investigator immediately if their female partner becomes pregnant. Pregnant subjects will be withdrawn from further trial treatment. The subjects will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the trial.

A pregnancy as such is not an AE, unless there is a possibility that the IMP has interfered with the efficiency of any contraceptive measures. However, the investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs, Section 12.17.1. The pregnancy report form should be used instead of the SAE form.

The pregnant subject or partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

12.17.6. Safety Management Plan

The process of SAE-Assessment is performed by Premier Research. In this context a study specific 'Safety Management Plan' has to be prepared before first subject is recruited into the study. The Safety Management Plan contains a detailed description of all procedures concerning the documentation and reporting of AEs, SAEs and SUSARs. Additionally, the Safety Management Plan describes the preparation of the Development Safety Update Report (DSUR), the Benefit-Risk-Assessment and the process of immediate actions to prevent the trial patients from immediate risks.

13. STATISTICS

A total of 30 subjects will be included. No formal sample size calculation was done as this is an initial pilot study.

On the basis of the poor historical success rates of current standard therapy, a 30% response rate for the primary endpoint would be considered clinically relevant.

Data will be presented descriptively and using 95% confidence intervals. Statistical analysis comparing post-treatment values with Baseline will be conducted for selected endpoints. As this is an exploratory study no adjustments for multiplicity will be done. Further details of all analyses will be given in the statistical analysis plan.

13.1. Primary Endpoint

- Sputum culture conversion defined as at least three consecutive negative sputum samples during the treatment period.

The time of culture conversion is defined as the time the first of three consecutive negative samples was obtained.

Sputum culture conversion rates (number of patients who convert to negative out of the number per group) will be presented with 95% exact binomial confidence intervals.

13.2. Secondary Endpoints

All endpoints that are of the form “conversion to negative” will be presented in the same way as the primary endpoint. This includes:

- Sputum smear conversion defined as at least three consecutive negative AFB stained sputum smears on microscopy during the treatment period in subjects that were smear positive at Baseline.
- Durability of sputum culture conversion (defined as conversion at or before Week 48 and culture still negative at 12-weeks follow-up).
- Durability of sputum smear conversion (defined as conversion at or before Week 48 and smear still negative at 12-weeks follow-up).

Semi-quantitative grading:

- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears will be cross-tabulated in 5-by-5 tables of negative, scant, 1+, 2+, or 3+ comparing Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up. The number of patients who decrease over the scale (and proportion out of the number per group) will be presented with 95% exact binomial confidence intervals.
- Change in semi-quantitative grade of sputum cultures will be cross-tabulated in a similar way comparing Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up. The number of patients who decrease over the scale (and

proportion out of the number per group) will be presented with 95% exact binomial confidence intervals.

All endpoints that are of the form "changes in quantitative assessments" will be presented as median, min and max at baseline and each assessment visit; and median, min and max change from Baseline to each assessment visit. This includes:

- Change in symptom scores (assessed using LRTI-VAS and QOL-B) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in GRH from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in body weight from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in 6MWD, oxygen desaturation and Borg CR10 scores during a 6MWT from Baseline to Week 12, 24, 48 and 12-week follow-up.

No "analysis sets" (intention to treat, per protocol, etc.) are being defined. All subjects will be included in the analyses/data presentations (equivalent to the Full Analysis Set).

Only recorded data will be analyzed/presented and any subjects who have missing data will only have observed data reported, with no imputation for missing data.

No interim analyses are planned.

Data listings will show all recorded data, separately by Group (as defined above).

13.3. Safety Endpoints

All AEs will be summarized in total and by Group 1 or Group 2.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT).

All serious AE and AEs leading to study withdrawal will be listed and individual-subject narratives written for all SAEs.

13.4. General

No "analysis sets" (intention to treat, per protocol, etc.) are being defined. All subjects will be included in the analyses/data presentations (equivalent to the Full Analysis Set).

Only recorded data will be analyzed/presented and any subjects who have missing data will only have observed data reported, with no imputation for missing data.

No interim analyses are planned.

Data listings will show all recorded data, separately by Group (as defined above).

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Access to Source Data and Documentation

The investigator should guarantee direct access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the IEC/IRB, if required.

14.2. Subject Records and Source Data

The origin of source data in the trial will be specified for each trial site in a separate document.

It is the responsibility of the investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the subject is in a clinical trial
- The identity of the trial e.g. Trial code
- Subject number
- That informed consent was obtained and the date
- Diagnosis
- Dates of all visits and telephone contacts with the subject during the trial period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of subject withdrawal
- Subject health service identification number

The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. After each subject visit, the eCRF should be completed in a timely manner. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Data recorded in the eCRFs will be monitored.

14.3. Study Monitoring

Regular monitoring visits will be performed according to International Conference on Harmonization (ICH) GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. In accordance with written standard operating procedures (SOP)s, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.4. Audits and Inspections

Authorized representatives of Savara, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Savara audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Savara immediately if contacted by a regulatory agency about an inspection.

14.5. Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The investigator must obtain IEC/IRB approval for the investigation. Initial IEC/IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the investigator and made available for inspection.

Any modification of the protocol must be documented in a protocol amendment and any amendment considered substantial requires approval/favorable opinion by the appropriate regulatory authority and IEC/IRB.

15. ETHICS

15.1. Ethics Review

This protocol and any amendments will be submitted to a properly constituted IEC/IRB, in accordance with the International Conference on Harmonization (ICH) guidelines, the applicable European Directives and local legal requirements, for approval/favorable opinion. An approval/favorable opinion must be obtained in writing before the first subject can be recruited.

15.2. Ethical Conduct of the Study

The trial will be conducted in compliance with the protocol, applicable regulatory requirements, GCP and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

16. DATA HANDLING AND RECORDKEEPING

16.1. Data Management

Data management and handling of data will be conducted according to the trial specific Data Management Plan with ICH guidelines and standard operating procedures (SOPs).

An eCRF system, will be used to capture data from the trial. Data entry will be performed by the trial site personnel. Validation and data queries will be handled by qualified Contract Research Organization (CRO) staff. The data will be subjected to validation according to a data validation plan in order to ensure accuracy in the collected eCRF data.

Changes to the data in the eCRF will be made at the site by delegated trial site personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data. Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the trial database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a trial specific Data Management Report.

16.1.1. Protocol Deviations

The instructions in the protocol must be followed. If deviations occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. Deviations must be documented. In addition, deviations must be accompanied by a description of the deviation, the relevant dates (start and stop) and the action taken. Deviation reports must be reported in the eCRF and supporting documentation must be kept in the investigator's file and in the trial master file.

16.2. Inspection of Records

The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16.3. Retention of Records

The investigator/institution should maintain essential documents (as defined in ICH E6 GCP, Section 8) as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval. If it becomes necessary for Savara or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

It is the responsibility of the sponsor to inform the investigator/institution in writing as to when the documents no longer need to be retained.

17. FINANCE AND INSURANCE

The sponsor must provide insurance or must indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice, negligence or non-compliance with the protocol.

The compensation to the investigators for work performed under this protocol will be set out in separate clinical trial agreements with the investigators.

18. TRIAL ORGANIZATION

The telephone numbers and fax numbers of relevant Sponsor staff are listed in the investigator site file.

The title, name, address and contact details of CROs, laboratories and other vendors are listed in Appendix 3.

19. PUBLICATION POLICY

Information about this clinical trial will be publicly registered on the website www.clinicaltrials.gov before the first subject enters into the trial.

A CTR will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

All information supplied by the sponsor in connection with this trial will remain the sole property of the sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the sponsor.

Savara is committed to data transparency by disclosing information from its research programs through presentations at scientific congresses and publication in peer-reviewed journals. Savara adheres to the International Committee of Medical Journal Editors (ICMJE) recommendations regarding authorship.

Draft manuscripts for joint publication will be prepared in collaboration between Savara, the coordinating Investigator and other Investigators, as appropriate depending on their contribution to the trial.

Investigators participating in this multicenter study may publish data subsets from their individual institution only after publication of the primary manuscript. Written permission to publish must be obtained from the sponsor in advance. As some of the information regarding the IMP and development activities at the sponsor may be of a strictly confidential nature, the sponsor must be given a 30-day period to review and approve any publication manuscript prior to their submission to journals, meetings or conferences. Such a manuscript should always reference the primary publication of the entire study.

The sponsor undertakes to publish the results in compliance with the joint position of the innovative pharmaceutical industry [Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases, available from http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/EN/November_10_2009] for public disclosure of clinical trial results in a free, publicly accessible database, regardless of outcome, no later than one year after the medicinal product is first approved and is commercially available in any country.

20. LIST OF REFERENCES

Aitken ML, Limaye A, Pottinger P, et al. Respiratory outbreak of Mycobacterium abscessus subspecies massiliense in a lung transplant and cystic fibrosis center. *Am J Respir Crit Care Med.* 2012;185(2):231-232.

Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am J Respir Crit Care Med,* 2012;185:881–6.

Aksamit TR, O'Donnell AE, Barker A, et al. Adult Bronchiectasis Patients: A First Look at the United States Bronchiectasis Research Registry. *Chest*. 2017;151(5):982-92.

Almeida R, D'Oliveira A, Jr., Machado P, et al. Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony-stimulating factor versus stibogluconate alone in the treatment of cutaneous Leishmaniasis. *J Infect Dis.* 1999;180(5):1735-1737.

Awuh JA, Flo TH. Molecular basis of mycobacterial survival in macrophages. *Cellular and molecular life sciences* : CMLS. 2017.

Bermudez LE, Martinelli J, Petrofsky M, Kolonoski P, Young LS. Recombinant granulocyte-macrophage colony-stimulating factor enhances the effects of antibiotics against Mycobacterium avium complex infection in the beige mouse model. *J Infect Dis*. 1994;169(3):575-580.

Bryant JM, Grogono DM, Rodriguez-Rincon D, et al. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium. *Science*. 2016;354(6313):751-757

Chatte G, Panteix G, Perrin-Fayolle M, Pacheco Y. Aerosolized interferon gamma for Mycobacterium avium-complex lung disease. *Am J Respir Crit Care Med*. 1995;152(3):1094-1096.

Choudhary GS, Yao X, Wang J, Peng B, Bader RA, Ren D. Human Granulocyte Macrophage Colony-Stimulating Factor Enhances Antibiotic Susceptibility of Pseudomonas aeruginosa Persister Cells. *Sci Rep*. 2015;5:17315.

Cowman S, Burns K, Benson S, Wilson R, Loebinger MR. The antimicrobial susceptibility of non-tuberculous mycobacteria. *J Infect*. 2016;72(3):324-331.

de Silva TI, Cope A, Goepel J, Greig JM. The use of adjuvant granulocyte-macrophage colony-stimulating factor in HIV-related disseminated atypical mycobacterial infection. *J Infect.* 2007;54(4):e207-210.

Fleetwood AJ, Cook AD, Hamilton JA. Functions of granulocyte-macrophage colony-stimulating factor. *Crit Rev Immunol*. 2005;25(5):405-428.

Graham B L, Brusasco V, Burgos F et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017; 49: 1600016

Griffith DE, Aksamit T, Brown-Elliott BA, et al. An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases. *Am J Respir Crit Care* Med. 2007;175(4):367-416.

Griffith DE, Aksamit TR. Understanding nontuberculous mycobacterial lung disease: it's been a long time coming. *F1000Res*. 2016;5:2797.

Hallstrand TS, Ochs HD, Zhu Q, Liles WC. Inhaled IFN-gamma for persistent nontuberculous mycobacterial pulmonary disease due to functional IFN-gamma deficiency. *Eur Respir J*. 2004;24(3):367-370.

Heidarieh P, Mirsaeidi M, Hashemzadeh M, et al. In Vitro Antimicrobial Susceptibility of Nontuberculous Mycobacteria in Iran. *Microb Drug Resist*. 2016;22(2):172-178.

Holland AE, Spruit MA, Troosters T et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Resp J*, 2014;44 (6):1428-1446

Kedzierska K, Mak J, Mijch A, et al. Granulocyte-macrophage colony-stimulating factor augments phagocytosis of Mycobacterium avium complex by human immunodeficiency virus type 1-infected monocytes/macrophages in vitro and in vivo. *J Infect Dis.* 2000;181(1):390-394.

Kemper CA, Bermudez LE, Deresinski SC. Immunomodulatory treatment of Mycobacterium avium complex bacteremia in patients with AIDS by use of recombinant granulocyte-macrophage colony-stimulating factor. *J Infect Dis*. 1998;177(4):914-920.

Lam PK, Griffith DE, Aksamit TR, et al. Factors Related to Response to Intermittent Treatment of Mycobacterium avium Complex Lung Disease. *Am J Respir Crit Care Med.* 2006.

Marras TK, Mendelson D, Marchand-Austin A, May K, Jamieson FB. Pulmonary nontuberculous mycobacterial disease, Ontario, Canada, 1998–2010. *Emerg Infect Dis.* 2013; 19: 1889–91.

Martino A. Mycobacteria and innate cells: critical encounter for immunogenicity. *J Biosci*. 2008;33(1):137-144.

Milanes-Virelles MT, Garcia-Garcia I, Santos-Herrera Y, Valdes-Quintana M, Valenzuela-Silva CM, Jimenez-Madrigal G*, et al.* Adjuvant interferon gamma in patients with pulmonary atypical Mycobacteriosis: a randomized, double-blind, placebo-controlled study. *BMC Infect Dis*. 2008; 8 (17)

Moser C, Jensen P, Pressler T, Holby N. Adjunctive treatment with granulocyte-macrophage colony simulating factor (GM-CSF) of CF patients with severe *Mycobacterium abscessus* lung infection. The 19th annual north american cystic fibrosis conference; 2005; Baltimore, Maryland.

Onyeji CO, Nightingale CH, Tessier PR, Nicolau DP, Bow LM. Activities of clarithromycin, azithromycin, and ofloxacin in combination with liposomal or unencapsulated granulocyte-macrophage colony-stimulating factor against intramacrophage Mycobacterium avium-Mycobacterium intracellulare. *J Infect Dis*. 1995;172(3):810-816.

Prevots DR, Shaw PA, Strickland D et al. Non-tuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. *Am J Respir Crit Care Med*. 2010: 182 (7): 970-976

Rawson TM, Abbara A, Kranzer K, et al. Factors which influence treatment initiation for pulmonary non-tuberculous mycobacterium infection in HIV negative patients; a multicentre observational study. *Respir Med*. 2016;120:101-108.

Ringhausen FC, Wagner D, deRoux A et al. Prevalence of Nontuberculous Mycobacterial Pulmonary Disease, Germany, 2009–2014. *Emerg Infect Dis*, 2016; 22(6): 1102-1105

Rose RM, Kobzik L, Dushay K, et al. The effect of aerosolized recombinant human granulocyte macrophage colony-stimulating factor on lung leukocytes in nonhuman primates. *The American review of respiratory disease.* 1992;146(5 Pt 1):1279-1286.

Rothchild AC, Jayaraman P, Nunes-Alves C, Behar SM. iNKT cell production of GM-CSF controls Mycobacterium tuberculosis. *PLoS pathogens*. 2014;10(1):e1003805.

Stout JE, Koh WJ, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. *Int J Infect Dis*. 2016; 45:123-134.

Thomson R, Donnan E, Unwin S. Nontuberculous Mycobacterial Lung Disease. Time to Get a Grip! *Ann Am Thorac Soc*. 2015;12(10):1425-1427.

Wassilew N, Hoffmann H, Andrejak C, Lange C (2016). Pulmonary Disease Caused by Non-Tuberculous Mycobacteria. *Respiration.* 2016; 91(5): 386-402.

Winthrop KL, Varley CD, Ory J, Cassidy PM, Hedberg K. Pulmonary disease associated with nontuberculous mycobacteria, Oregon, USA. *Emerg Infect Dis.* 2011;17(9):1760-1761.

Zhao X, Wang Y, Pang Y. Antimicrobial susceptibility and molecular characterization of Mycobacterium intracellulare in China. *Infect Genet Evol*. 2014;27:332-338

21. APPENDICES

APPENDIX 1. RATIONALE FOR AMENDMENTS AND LIST OF REVISIONS

Table 4: Table of Revisions

Date	Version	Description of Document	Rationale for changes
27-Sep-2017	1.0	Final Protocol	
12-Nov-2017	2.0	Amendment 1 to the protocol. Section 2. Synopsis The synopsis was updated with the following: - Study timelines updated to reflect the current estimations. - Inclusion criterion 5 corrected. Double-blind trial treatment changed to trial treatment. - NTM PCR endpoint and assessments removed. - A semi-quantitative assessment of sputum cultures added as an endpoint. Section 3. Trial Flow Chart - Subject diary was added. Section 6.1 Background - Updated information on ongoing clinical trial in PAP including the most recent DSMB review. Section 6.2 Trial Rationale - Revised some of the background literature information to be more informative and better aligned with source information. Section 7.3 Endpoints - Endpoints updated. NTM PCR endpoint removed - A semi-quantitative assessment of sputum cultures added as an endpoint. Section 8.1 Overall Trial Design - Text on PCR removed Section 8.1.1 Trial Period - Study timelines updated to reflect the current estimations. Section 8.1.3 Trial Completion - Definition of trial completion added.	The protocol was amended on the 12-Nov-2017 (Amendment 1 to the protocol) before the protocol was submitted to any CA or IEC. Reason for the changes was not provided as protocol version 1.0 had not been in use. Amendment 1 to the protocol is considered substantial

Date	Version	Description of Document	Rationale for changes
		Section 8.2 Number of Subjects - Text updated to clarify wording. Section 9 Selection and Withdrawal of Subjects - Intro text included to specify that the subject must fulfil all inclusion and none of the exclusion criteria. Section 9.1 - Inclusion criterion 5 corrected. Double-blind trial treatment changed to trial treatment. Section 10.5 Subject Identification Lists - Text updated to specify that the investigator must maintain a log of all screened subjects. Section 12.2 Collection of Sputum Samples for Microbiological Characterization and Quantification - A semi-quantitative assessment of the sputum culture was added. Quantitative PCR taken out but described that samples will be stored for potential post-hoc analysis. Section 12.6 Subject Diary - Section on subject diaries was added. - Section 13.2 Secondary Endpoints - Statistical methods updated to correspond with changes in assessments and secondary endpoints. Section 12.13.1 DLCO - Calculation of DLCO clarified Section 13.2 Secondary Endpoints - Endpoints updated. NTM PCR endpoint removed - A semi-quantitative assessment of sputum cultures added as an endpoint. Section 20 List of References - Some references taken out in line with revisions to Section 6.2.	
22-Aug-2018	3.0	Amendment 2 to the protocol. Section 2. Synopsis The synopsis was updated with the following: - Number of collected sputum samples	Amendment 2 to the protocol is considered substantial The rational for the changes is the following

Date	Version	Description of Document	Rationale for changes
		changed to 3 samples at all visits. - Definition of sexual abstinence added to inclusion criterion 5 - Anti-drug-antibodies change to Anti-GM-CSF-antibodies under assessments. - Flow chart updated to reflect that 3 sputum samples will be collected at each visit Section 8.1 Overall Trial Design - Number of collected sputum samples changed to 3 samples at all visits. Section 9.1 Subject Inclusion Criteria - Definition of sexual abstinence added to the inclusion criterion 5 Section 11.5 Administration - Text updated to clarify that study treatment should not be taken prior to visit 3 and 5. Section 12.2 - Number of collected sputum samples changed to 3 samples at all visits. Section 12.14.1 - Text changed from Anti-drug-antibodies to Anti-GM-CSF Spelling and formatting errors and was	The number of sputum samples pr. visit is increased to strength the validity and robustness of the microbiological assessments. Definition of sexual abstinence was added after a request from the competent authority in UK (MHRA). Anti-drug-antibodies was changed to anti-GM-CSF to specify the actual analysis performed. Text in section 11.5 wrongly stated that blood sampling should be done before IMP dosing at visit 3 and 4.
26-Sep-2018	4.0	Section 2. Synopsis The synopsis was updated with the following: - Study period dates were revised to reflect the longer treatment duration - Additional visits at 4-week intervals: 32, 36, 40, 44, 48. The visits at Weeks 32, 40 and 48 will include a clinic visit and the visits at Weeks 28, 36 and 44 will include telephone contact - Details of visits at which each assessment was performed was revised - Update on safety review provided - One grading changed from scant to occasional to align with the naming at laboratory - Safety laboratory sample added at the 12-weeks follow-up visit. - Duration of treatment was prolonged to 48 weeks - Study endpoints were revised to allow for data from the additional visits and assessments Section 3.0. Trial Flow Chart	Treatment period is to be extended by 24 weeks to a total of 48 weeks Protocol wording updated to reflect that the safety review meeting has taken place. Dose modifications allowed after sponsor approval in case of intolerance in order to maintain subjects on treatment if deemed feasible by the investigator. CT scan added at visit 14. CT scans should only be performed if this is already a part of local standard at the site. Safety laboratory sampling added at the 12-week follow-up visit in order to assess the laboratory parameters

Date	Version	Description of Document	Rationale for changes
		- Revised to detail additional visits and assessments - CT scan added as an optional procedure at V14 - Safety laboratory sample added at the 12-weeks follow-up visit. Section 6.2. Trial Rationale - The treatment duration was revised and update on the safety review was provided Section 7.3. Endpoints - Study endpoints were revised to allow for data from the additional visits and assessments Section 8.1. Overall Trial Design - Additional visits at 4-week intervals: 32, 36, 40, 44, 48. The visits at Weeks 32, 40 and 48 will include a clinic visit and the visits at Weeks 28, 36 and 44 will include telephone contact - Details of visits at which each assessment was performed was revised - Duration of treatment was revised - Update on the safety review was provided Section 8.1.1. Trial Period - Dates were revised to reflect the longer treatment duration Section 8.4 - Update from the safety was provided - Dose reductions allowed in case of poor tolerability Section 9.3.2. Withdrawal from the Trial - Revised required assessments to those conducted at Week 48 Section 11.3 Study Drug Storage - Revised in line with additional visits and extended treatment duration Section 11.5 Administration - Revised in line with additional visits and extended treatment duration Section 12.2 Collection of Sputum Samples for Microbiological Characterization and Quantification - Revised in line with additional visits and extended treatment duration. Detailed three samples are to be collected at home for the	after 12-weeks off IMP treatment.

Date	Version	Description of Document	Rationale for changes
		telephone contact visits - One grading changed from scant to occasional to align with the naming at laboratory Section 12.7 Adverse Events - Revised in line with additional visits and extended treatment duration. Section 12.14 Laboratory Assessments - Revised total volume of blood to 240 mL due to additional visits and extended treatment duration. Section 12.16 Adverse Events - Revised in line with additional visits and extended treatment duration. Section 13 Statistics - Study endpoints were revised to allow for data from the additional visits and assessments - One grading changed from scant to occasional to align with the naming at laboratory	

APPENDIX 2. SIGNATURE PAGE

This Clinical Trial Protocol is approved by:

BIOSTATISTICIAN Date:
Simon Day, PhD Director Clinical Trials and Training Ltd
SPONSOR TRIAL DIRECTOR Date:
Mikkel Walmar, MSc, Pharm Manager, Clinical Operations Savara ApS **SPONSOR MEDICAL EXPERT** Date:
Cecilia Ganslandt MD Vice President, Head of Clinical Development, Savara ApS Slotsmarken 17 2970 Hørsholm, Denmark +45 79301413

APPENDIX 3. TRIAL ORGANIZATION

Central Laboratory (Safety Laboratory Analysis):
Name: BARC Global Central Laboratory
Address: Industriepark Zwijnaarde 3, 9052 Ghent, Belgium
Phone: +32 9 329 23 29

Reference Laboratory (Anti-GM-CSF analysis):
Name: IPM Biotech GmbH
Address: Lademannbogen 10, 22339 Hamburg,
Phone: +49 40 5267790

Reference Laboratory (Microbiology analysis Australia):
Name: Sullivan Nicolaides Pathology
Address: 24 Hurworth St, Bowen Hills, QLD 4006
Phone number: +61 07 3377 8666

Reference Laboratory (Microbiology analysis UK):
Name: Royal Brompton Hospital
Address: Sydney St, Chelsea, London SW3 6NP, UK
Phone number: +44 20 7352 8121

CRO (Submissions, Monitoring, Data Management and Statistics):
Name: Southern Star Research
Address: Level 1, 1 Merriwa Street, Gordon NSW 2072, Australia. Postal: PO Box 52, Gordon NSW 2072 Australia
Phone: +61 2 9011 6266

Manufacturing:
Name: Miltenyi Biotec GmBH
Address: Robert-Koch-Straße 1, 17166 Teterow, Germany
Phone: +49 2204 8306-0

Packaging/labelling of IMP:
Name: KLIFO A/S
Address: Smedeland 36, 2600 Glostrup
Phone: +45 44 22 29 00

Pharmacovigilance
Name: Premier Research
Address: 1st Floor, Rubra 2, Mulberry Business Park, Wokingham, RG41 2GY, UK
Phone: +44 118 936 4000

APPENDIX 4. QUESTIONNAIRES

4.1 Borg CR10 Scale

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	**Extremely strong**	**"Maximal"**
11		
✦		
●	Absolute maximum	Highest possible

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

4.2 Quality of Life Questionnaire – Bronchiectasis

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

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

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

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

Demographics *Please fill in the information or tick the box to indicate your answer.*

A. What is your date of birth?

Date ☐☐ ☐☐ ☐☐☐☐
Day Month Year

B. What is your gender?

☐ Male ☐ Female

C. During the **past week**, have you been on holiday or not studying or working for reasons **NOT** related to your health?

☐ Yes ☐ No

D. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ Living with a partner

E. Which of the following best describes your ethnic group?

- ☐ White
- ☐ Mixed/multiple ethnic groups
- ☐ Asian/Asian British
- ☐ Black/African/Caribbean/Black British
- ☐ Other (please describe) _____
- ☐ Prefer not to answer this question

F. What is the highest level of education you have completed?

- ☐ Some secondary school or less
- ☐ GCSEs/Standard Grades or equivalent
- ☐ A Level/Higher/Advanced Higher or equivalent
- ☐ Some college or university
- ☐ College qualification (e.g. HNC, HND, Foundation Degree)
- ☐ Undergraduate degree (e.g. BA, BSc)
- ☐ Postgraduate degree (e.g. MA, MSc, PhD)

G. Which of the following best describes your current work or educational status?

- ☐ Studying outside the home
- ☐ Studying at home/distance learning
- ☐ Seeking work
- ☐ Working full-time or part-time (either outside the home or at a home-based business)
- ☐ Full-time housewife/househusband
- ☐ Not studying or working due to my health
- ☐ Not working for other reasons/Retired

Continue to Next Page

 QOL-B, Version 3.1 Page 1

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section I. Quality of Life

Please tick a box to indicate your answer.

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

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

Are you currently on any treatments (such as: oral or inhaled medications; a PEP, Acapella® or Flutter® device; chest physiotherapy; or Vest) for bronchiectasis?

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

Please circle a number to indicate your answer. Please choose only one answer for each question.

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

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

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

Continue to Next Page

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Please circle a number to indicate your answer. Please choose only one answer for each question.

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

Please tick a box to indicate your answer.
Thinking about your health during the past week, indicate the extent to which each sentence is true for you.

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

Please circle a number or tick a box to indicate your answer.

During the past week:

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

	Always	Often	Sometimes	Never
28. How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?	☐	☐	☐	☐

Continue to Next Page

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section II. Respiratory Symptoms

Please tick a box to indicate your answer.

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

32. Has your sputum been mostly:

☐ Clear ☐ Clear to yellow ☐ Yellowish-green
☐ Brownish-dark ☐ Green with traces of blood ☐ Don't know

How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath when being more active, such as when doing housework or gardening?	☐	☐	☐	☐
34. Have you had wheezing?	☐	☐	☐	☐
35. Have you had chest pain?	☐	☐	☐	☐
36. Have you had shortness of breath when talking?	☐	☐	☐	☐
37. Have you woken up during the night because you were coughing?	☐	☐	☐	☐

Please make sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

4.3 Lower Respiratory Tract Infections –Visual Analogue Scale – for use in non-CF Bronchiectasis