MOLGRAMOSTIM NEBULIZER SOLUTION

CLINICAL TRIAL PROTOCOL

SAV008-02

An Op**E**n-label, **N**on-controlled, Multi**C**enter, Pil**O**t Trial, using Inhaled Molgramostim in Cystic Fib**R**osis Subjects with Nontuberculous Mycobacterial (NTM) Inf**E**ction
(ENCORE)

Product Name:	**Molgramostim Nebulizer Solution (Molgradex®) 300 µg**
Indication:	**Pulmonary NTM infection**
Phase:	**IIA**
EudraCT No.	**N/A**
IND Number:	**139376**
Sponsor:	**Savara Inc** **6836 Bee Cave Road, Building 3, Suite 200** **Austin, TX, 78746** **United States**
Date of Protocol:	**12-DEC-2019**
Version:	**3.0**

Protocol Signature Page

This Clinical Trial Protocol is approved by:

BIOSTATISTICIAN Date:
Lars Korsholm, PhD Director, Biostatistics Savara Aps.
SPONSOR TRIAL MANAGER Date:
Amy Beasley, MPH Manager, Clinical Operations Savara Inc. **SPONSOR MEDICAL EXPERT** Date:
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PROTOCOL AGREEMENT

Protocol Title:	An Open-label, Non-controlled, Multicenter, Pilot Trial, using Inhaled Molgramostim in Cystic Fibrosis Subjects with Nontuberculous Mycobacterial (NTM) Infection
Trial Code:	SAV008-02
Protocol Version:	3.0
Protocol Date:	12DEC2019

I confirm that I have received the abovementioned protocol.

By signing below, and in accordance with ICH GCP, I confirm that I:

- Will personally conduct or supervise the trial
- Will ensure that the trial is conducted in compliance with ICH GCP
- Assume responsibility for the proper conduct of the trial in accordance with the approved protocol
- Will ensure that site staff assisting with the trial are adequately informed about this protocol
- Will maintain adequate and accurate source documents and trial records, and will make those records available for inspection and audit

Investigator Signature	**Date of Signature**
Investigator Printed Name	**Site Number**

1. SYNOPSIS

Name of Sponsor/Company:
Savara Inc.

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

Name of Active Ingredient:
Molgramostim (recombinant human Granulocyte Macrophage Colony Stimulating Factor [rhGM-CSF])

Title of Study: An Open-label, Non-controlled, Multicenter, Pilot Trial, using Inhaled Molgramostim in Cystic Fibrosis Subjects with Nontuberculous Mycobacterial (NTM) Infection

Study center(s): A sufficient number of centers located in, but not necessarily limited to, the United States of America (USA).

US Lead Investigator: Jerry A. Nick, MD, National Jewish Health, Denver, CO.

Study period:	**Phase of development:**
Trial duration for each subject is 72 weeks (48 weeks Treatment period and 24 weeks Follow-up period)	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 pulmonary function.
- To investigate efficacy of inhaled molgramostim on patient reported outcomes.
- To investigate efficacy of inhaled molgramostim on body mass index (BMI).
- To investigate safety of inhaled molgramostim in subjects with NTM infection

Exploratory:

- To investigate efficacy in subjects infected with *M. abscessus* complex (MABSC) and *M. avium* complex (MAC), respectively.
- To investigate efficacy in subjects on concurrent anti-mycobacterial treatment and subjects not on anti-mycobacterial treatment, respectively.
- To investigate rates of recurrence and reinfection after End of Treatment.
- To investigate efficacy of inhaled molgramostim on bacterial co-infections.

- To investigate efficacy of inhaled molgramostim on frequency of pulmonary exacerbations.
- To investigate efficacy of inhaled molgramostim on morphologic findings on computed tomography (CT) scans of the lung.

Methodology:

The Screening period will begin up to 10 weeks prior to the Baseline visit for collection of the sputum sample, but the remainder of the assessments including safety labs will be completed within 6 weeks of Baseline, to determine eligibility. Adult subjects with a history of cystic fibrosis (CF) and chronic pulmonary NTM infection will be considered for enrollment. Chronic pulmonary NTM infection will be defined by at least three positive NTM cultures (sputum or broncho-alveolar lavage (BAL)) for the same species/subspecies of MAC or MABSC within the 2 years prior to screening, with at least one positive within the past 6 months prior to screening and a minimum of 50% of NTM cultures positive over the past 2 years. Subjects must additionally provide a positive sputum culture with the same species/subspecies obtained from the central laboratory during the Screening period to be eligible

Three groups of subjects will be recruited:

- Group 1: Subjects with chronic pulmonary MAC or MABSC infection who have not consistently achieved negative NTM sputum cultures while currently on a multidrug NTM guideline-based antimycobacterial regimen, which has been ongoing for at least 9 months prior to the Baseline visit.
- Group 2: Subjects with chronic pulmonary MAC or MABSC infection 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.
- Group 3: Subjects with chronic pulmonary MAC or MABSC - infection not meeting recommendations for treatment with a multidrug NTM guideline-based antimycobacterial regimen based on failure to meet American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for NTM pulmonary disease (*i.e.* absence of radiologic findings and clinical symptoms beyond what is expected from underlying CF).

All subjects will have Screening, Baseline, Week 1, 2 and followed by monthly Treatment visits from week 4 during the Treatment period. The Treatment period will be 48 weeks. Following the End of Treatment (Week 48), subjects will have a Follow-up visit at 4 and 12 weeks, and the End of Study visit 24 weeks after the End of Treatment. At the Baseline visit, eligible subjects will start treatment with inhaled molgramostim. A detailed Schedule of Assessments is outlined in Table 1. At each visit any changes in concomitant medication 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. If needed, unscheduled visits will be conducted at the Investigator's discretion. All subjects will be maintained on their standard CF treatment and medications independent of NTM treatment status.

Treatment with inhaled molgramostim will be given at a dosage of 300 µg once daily for 48 weeks. Dosing will be done in the morning, after completion of the subject's normal airway clearance routine, where medications should be taken in the following order: bronchodilator, dornase alfa (Pulmozyme), inhaled antibiotics (e.g. TOBI) and lastly inhaled molgramostim.

Subjects on a cyclical on-off anti-Pseudomonal regimen will have their trial visits (Baseline and subsequent visits in the Treatment Period) scheduled during a week after at least three weeks off-treatment or after at least one week on-treatment of the antibiotic. Subjects on a continuous inhaled regimen, including continuous alternating therapy (CAT), should have been on a stable regimen for at least 28 days prior to Baseline.

A data review will be conducted after the first 6 subjects have completed 12 weeks of treatment. If safety concerns or poor tolerability are identified in this review, the review committee may decide on less frequent dosing for subsequent subjects in the study. Additional safety reviews will be conducted at regular intervals thereafter. During the study, subjects in Group 1 will continue use of antimycobacterial treatment, whereas subjects in Groups 2 and 3 will receive inhaled molgramostim as monotherapy for their NTM infection. For subjects in Group 1, the antimycobacterial therapy should preferably not change during the treatment period except in case of drug toxicity or adverse reactions. Antibiotics discontinued due to toxicity may be replaced, with drug selection and dose modification at the discretion of the treating physician. All changes in antimycobacterial treatment will be recorded, including reasons for each change. In the event the Investigator has evidence of infection while on treatment which requires more intensive therapy (i.e. additional antibiotics in Group 1 or addition of antibiotics to Group 2 or 3) the subject may be allowed to continue after discussion with the Sponsor medical monitor.

Number of subjects (planned):

No formal sample size calculation was done as this is an initial pilot study. To be able to assess response in each of the three groups, a minimum of 8 subjects with MAC or MABSC will be enrolled into each of the 3 groups, and a minimum of 30 subjects will be enrolled across all 3 groups. The maximum number of subjects enrolled into each group will be 12, and the maximum number of subjects enrolled into the study will be 34.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Written informed consent obtained from participant.
2. Confirmed diagnosis of CF according to the Cystic Fibrosis Foundation (CFF) 2017 Consensus Guidelines.
3. History of chronic pulmonary infection with *M. avium* complex (MAC) or *M. abscessus* complex (MABSC) (defined as at least three positive NTM cultures (sputum or BAL for the same species (MAC) or subspecies (MABSC) within the 2 years prior to the screening visit, with at least one positive within the past 6 months and a minimum of 50% of NTM cultures positive over the past 2 years) that does not demonstrate response to current treatment course based on decreasing NTM burden or frequency of positive cultures, and in the opinion of the Investigator is unlikely to resolve with current treatment course.
4. Subject fulfills criteria for inclusion in one of the following groups:
   - Group 1: Subject with chronic pulmonary MAC or MABSC infection currently on a multidrug NTM guideline-based antimycobacterial regimen, which has been ongoing for at least 9 months prior to the Baseline visit.
   - Group 2: Subject with chronic pulmonary MAC or MABSC infection who has stopped a multidrug NTM guideline-based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance.
   - Group 3: Subjects with chronic pulmonary MAC or MABSC - infection not meeting recommendations for treatment with a multidrug NTM guideline-based antimycobacterial regimen based on failure to meet ATS/IDSA criteria for NTM pulmonary disease (i.e. absence of radiologic findings and clinical symptoms beyond what is expected from underlying CF).
5. Ability to produce sputum or be willing to undergo an induction protocol that produces sputum for clinical evaluation.
6. An additional sputum culture performed by the central laboratory, which is positive for the same species (MAC) or subspecies (MABSC) of NTM as before the trial within 10 weeks of Baseline.
7. CF which in the Investigator's opinion is clinically stable and not expected to require lung transplantation within the next year.
8. $FEV_1 \geq 30\%$ of predicted at screening that is normalized for age, gender, race, and height, using the Global Lung Function Initiative (GLI) equation.
9. Subjects who are co-infected with a respiratory pathogen, e.g. *P. aeruginosa* or *S. aureus*, must either be stable on a regular suppression antibiotic regimen or must be, in the opinion of the Investigator, stable despite the lack of such treatment.
10. Female or male ≥18 years of age.
11. If female, subjects 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) during and until 30 days after last

dose of trial treatment, having 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.

For purposes of this study, the Sponsor defines "acceptable methods of contraception" as:

- Oral birth control pills administered for at least 1 monthly cycle prior to administration of the study drug.
- A synthetic progestin implanted rod (eg, Implanon®) for at least 1 monthly cycle prior to the study drug administration but not beyond the 4th successive year following insertion.
- Intrauterine devices (IUDs), inserted by a qualified clinician for at least 1 monthly cycle prior to study drug administration.
- Medroxyprogesterone acetate (eg, Depo-Provera®) administered for a minimum of 1 monthly cycle prior to administration of the study drug and continuing through 1 month following study completion.
- Hysterectomy or surgical sterilization.
- Vasectomized partner
- Abstinence.

Double barrier method (diaphragm with spermicidal gel or condoms with contraceptive foam) is not considered an acceptable form of contraception.

NOTE: For subjects prescribed Orkambi: Orkambi may substantially decrease hormonal contraceptive exposure, reducing the effectiveness and increasing the incidence of menstruation-associated adverse reactions. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.

12. If male, subjects who, if sexually active of reproductive potential and non-sterile (i.e., male who has not been sterilized by vasectomy for at least 6 months and not diagnosed with infertility through demonstration of azoospermia in a semen sample and/or absence of vas deferens through ultrasound) are willing to use a barrier method of contraception, or their female partner must use an acceptable method of contraception, during the study and until 30 days after last dose of medication.
13. 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.

Exclusion criteria:

1. Use of non-maintenance antibiotic for a concurrent pulmonary or extrapulmonary infection within 28 days prior to the Baseline visit.
2. Use of a maintenance antibiotic regimen containing azithromycin for a concurrent non-NTM pulmonary infection within 28 days prior to the Baseline visit. For subjects in Group 1, azithromycin is allowed if part of ongoing multidrug NTM guideline-based antimycobacterial regimen.

3. Prior therapy with inhaled or systemic granulocyte macrophage colony stimulating factor (GM-CSF).
4. Subjects with hemoptysis of ≥60 mL in a 24-hour period within 4 weeks prior to Screening.
5. Life expectancy of less than 6 months according to Investigator's judgement.
6. History of, or present, myeloproliferative disease, leukemia or other hematological malignancy.
7. Active pulmonary malignancy (primary or metastatic); or any malignancy requiring chemotherapy or radiation therapy within 1 year prior to Screening or anticipated during the study period.
8. Active autoimmune disorder or other condition requiring therapy associated with significant immunosuppression, e.g such as systemic corticosteroids at a dose equivalent of 10 mg/day or more of prednisolone or other significant immunosuppressant medications, within 3 months prior to Screening or anticipated during the study period. Inhaled or topical corticosteroids, or brief courses (< 14 days) of systemic corticosteroids for pulmonary exacerbations or other self-limited conditions are permitted.
9. Changes in antimicrobial, bronchodilator, anti-inflammatory or corticosteroid medications, or changes in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators, within 28 days prior to the Baseline visit.
10. Pulmonary tuberculosis requiring treatment or treated within 2 years prior to Screening.
11. History of human immunodeficiency virus (HIV) infection or other disease associated with significant immunodeficiency.
12. History of lung or other solid organ transplantation or currently on the list to receive lung or other solid organ transplantation.
13. History of congestive heart failure (CHF) New York Heart Association (NYHA) Class III or greater in severity.
14. History of cardiovascular ischemic event within 6 months of Baseline.
15. Any change in chronic NTM multi-drug antimycobacterial regimen within 28 days prior to Screening.
16. Treatment with any investigational medicinal product within 28 days of Screening.
17. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product.
18. Any other condition that, in the opinion of the Investigator, would preclude informed consent or assent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Investigational product, dosage and mode of administration:

Investigational Medicinal Product (IMP): Molgramostim nebulizer solution

Active Substance: Molgramostim (rhGM-CSF)

Pharmaceutical form: Nebulizer solution

Dosage: 300 µg once daily

Route of administration: Inhalation

Inhalation device: Investigational eFlow Nebulizer System (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:

- NTM sputum culture conversion to negative (defined as at least three consecutive negative mycobacterial cultures collected at least 4 weeks apart during the Treatment period).

Secondary Endpoints:

- NTM sputum culture microbiological cure (defined as multiple consecutive negative but no positive cultures with the causative species after last culture conversion and until the End of Treatment (Week 48).
- Time to first NTM sputum culture conversion during the Treatment period.
- Sputum smear conversion to negative (defined as at least three consecutive negative acid-fast bacilli (AFB) stained sputum smears on microscopy, collected at least 4 weeks apart in subjects who were smear positive at Baseline) during the Treatment period.
- Consistent sputum smear conversion to negative (defined as multiple consecutive negative but no positive smears after last smear conversion and until the End of Treatment (Week 48) in subjects who were smear positive at Baseline).
- Time to first NTM sputum smear conversion during the Treatment period.
- Durable NTM sputum microbiological cure for the NTM isolate(s) treated without recurrence at Week 12 after End of Treatment.
- Durable NTM sputum smear conversion to negative without subsequent positive smears at Week 12 after End of Treatment.
- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to End of Treatment and Week 12 after End of Treatment.
- Absolute change in FEV_1 (percent predicted) from Baseline to End of Treatment and Week 12 after End of Treatment.

- Change in respiratory domain score assessed by Cystic Fibrosis Questionnaire-Revised (CFQ-R) from Baseline to End of Treatment and Week 12 after End of Treatment.
- Change in BMI from Baseline to End of Treatment and Week 12 after End of Treatment.

Exploratory Endpoints:

- Change from Baseline in time to positivity on NTM liquid culture media at Treatment visits and Follow-up.
- Change in semi-quantitative grade of sputum cultures from Baseline to Treatment visits and Follow-up.
- Number of subjects with recurrence (re-emergence of the treated NTM species after End of Treatment), or reinfection (emergence of a different NTM species, after End of Treatment).
- Eradication and/or reduction in bacterial load of co-infections in sputum.
- Frequency of pulmonary exacerbations compared to the previous year.
- Change in CFQ-R domains scores for physical functioning, vitality, health perceptions, treatment burden, role functioning, emotional functioning, and social functioning.
- Change in CT scans of the lung from Baseline to End of Treatment (Week 48).

Safety:

- Number of AEs, serious adverse events (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 Treatment visits.
- A clinically significant decrease in FEV_1 (% predicted) from Baseline to Treatment visits that does not respond to typical CF treatment (including treatment of pulmonary exacerbation if suspected) and in the judgement of the Investigator is not due to typical complication of CF (*i.e*. acute pulmonary exacerbation).
- GM-CSF levels during Treatment period.
- Development of anti-drug antibodies during Treatment period and Follow-up period.

Methods of Assessment

Microbiological characterization and quantification – Microbiological assessments will be conducted at a specialized central laboratory. Sputum culture will be done on liquid and solid media to confirm growth or absence of growth of NTM. The time to positivity on liquid media and semi-quantitative assessment of bacterial load will be explored.

Samples will additionally be stored for potential quantitative polymerase chain reaction (PCR) analysis. These data may be reported separately, outside of the clinical trial report.

Identification to NTM species level (MAC) or subspecies (MABSC) will be conducted on positive samples using established methods. Isolates from selected samples may further be subject to molecular identification to the subspecies level, and whole genome sequencing to track potential

polyclonal infections and/or new acquisition of NTM infection during the follow-up period as part of a separate research protocol. These data may be reported separately, outside of the clinical trial report.

Using AFB staining (Fluorescence and/or Ziehl–Neelsen [ZN] stain), NTM in sputum will be identified and a semi-quantitative assessment of bacterial load (graded as 0, scant, 1+, 2+, 3+) will be conducted.

Routine CF bacteriology and fungal culture will be done locally on one sputum sample per visit.

Subject Reported Outcomes – clinical symptoms will be assessed using the CFQ-R questionnaire.

Radiology CT scans of the lung will be conducted per institutional standard of care technique, and images - will be uploaded into the eCRF. A scoring system for central reading of the scans will be defined at a later timepoint. If a chest X-ray 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.

PK and Anti-drug antibodies – A specialized central laboratory will be used for analysis of GM-CSF levels and anti-drug antibodies.

Pulmonary function testing (PFT) –Spirometry will be performed and in accordance with the current ATS recommendations for the performance and interpretation of tests.

Participants who routinely use bronchodilators should use them consistently throughout the study. Standard guidelines are noted below as a reference:

- Participants who routinely use short acting inhaled bronchodilators should use them 15 minutes to 2 hours prior to PFTs.
- Participants who routinely use long acting bronchodilator agents should use them 15 minutes to 6 hours prior to PFTs.

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

Statistical methods:

Each group (Group 1, Group 2 and Group 3) will be analyzed separately. Data will be presented descriptively and using 95% confidence intervals (CIs). Statistical summaries comparing post-treatment values with Baseline will be conducted for selected endpoints. For the time until sputum culture and smear conversion, Kaplan-Meier survival curves will be prepared.

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.

2. TRIAL FLOW CHART

Table 1: Study Schedule of Assessments

	Screening	Baseline	Treatment Period													End of Treatment (EOT)	Follow-up (FU)		End of Study	Unscheduled
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**UV**
Study Week	**-10 to -1 [d]**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**FU4**	**FU12**	**FU24**	**[a]**
Day	**-70 to -7**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**				
Window (days)			**±3**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
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	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	X	X	X	X
Pregnancy test and contraceptive check	X	X[m]			X	X	X	X	X	X	X	X	X	X	X	X	X			(X)
Physical exam/Brief Exam	X		X[l]	X[l]	X		X			X			X			X			X	(X)

	Screening	Baseline	Treatment Period													End of Treatment (EOT)	Follow-up (FU)		End of Study	Unscheduled
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**UV**
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Window (days)			**±3**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Vital signs	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X	X	X[j]	X	X	X[j]	X	X	X[j]	X	X	X	(X)
ECG	X	X			X		X			X			X			X			X	(X)
PFTs [b]	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collection of sputum sample for microbiology	X[c,d]	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[c]	(X)
Laboratory safety sampling	X	X[i]	X[k]	X[k]	X[i]	X	X[i]	X	X	X[i]	X	X	X[i]	X	X	X[i]	X	X	X	(X)
Samples for GM-CSF and anti-GM-CSF antibodies		X[e]		X[e]			X[e]			X[e]			X[e]			X [e]		X	X	(X)
CT[f]		X														X				(X)
Questionnaire CFQ-R		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Subject Diary Dispensed	X	X			X	X	X	X	X	X	X	X	X	X	X	X				
Trial drug administration training[g]		X																		(X)
Trial drug dosing at site		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]				(X)
Dispense trial drug		X			X	X	X	X	X	X	X	X	X	X	X					(X)

	Screening	Baseline	Treatment Period													End of Treatment (EOT)	Follow-up (FU)		End of Study	Unscheduled
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**UV**
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Window (days)			**±3**	**±3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Return of used trial drug					X	X	X	X	X	X	X	X	X	X	X	X				(X)
Compliance			X	X	X	X	X	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	X	X	X	X

Abbreviations: PFT=pulmonary function test; AE=adverse event; CFQ-R= Cystic Fibrosis Questionnaire-Revised; CT= Computed tomography; ECG= electrocardiogram; GM-CSF=granulocyte macrophage colony stimulating factor;

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

[b] Pulmonary function tests (FEV_1, FVC and FEV_1/FVC). At Baseline, PFTs will be performed pre-dose and post dose according to section 11.12.1.

[c] Two additional sputum samples collected for NTM culture will be collected at home preferably on consecutive days and within 5 days of the site visit.

[d] The screening NTM sample may be collected up to 10 weeks prior to baseline, after collection of informed consent. The remainder of screening visit should occur within 6 weeks of the Baseline visit.

[e] Samples for GM-CSF and anti-GM-CSF antibodies to be taken before dosing at the site. An additional sample for GM-CSF to be taken approximately 2 hours post dose for subjects that remain on IMP.

[f] A CT scan of the lung performed up to 6 months prior to the Baseline visit is acceptable. If Early End of Treatment Visit occurs prior to or at Week 12, then a CT scan is not required at End of Treatment. In case of a clinically significant drop in FEV_1 not responding to standard CF care, the CT scan may be repeated. If a chest radiograph is done information on the results will be collected.

[g] Re-training can take place at all visits in the treatment period

[h] Trial drug dosing should be performed after blood sampling.

[i] Safety laboratory samples to be taken before dosing at the site. White blood cell count (WBC) and differentials to be repeated approximately 2 hours post dose for subjects that remain on IMP.

[j] Repeat vital signs approximately 2 hours post dosing for subjects that remain on IMP.

[k] CBC with differential will be collected pre-dose and approximately 2 hours post dose at visits 3 and 4. No additional safety laboratory assessments will be collected at this visit.

[l] For Week 1 and 2, Brief exam of lungs and symptom oriented physical exam should be performed.

[m] A urine pregnancy test will be performed for females in addition to the serum pregnancy test at the baseline visit.

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4. 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
AFB	Acid Fast Bacilli
aPAP	Autoimmune Pulmonary Alveolar Proteinosis
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
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
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Competent Authority
CAT	Continuous Alternating Therapy
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CHF	Congestive Heart Failure
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
CT	Computer Tomography
CTR	Clinical Trial Report

Abbreviation or Specialist Term	Explanation
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFD	Embryo Fetal Development
eGFR	Estimated Glomerular Filtration Rate
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
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDSA	Infectious Diseases Society of America
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous
LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
MABSC	*M. abscessus* Complex
MAC	*M. avium* Complex
MAD	Multiple Ascending Dose
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
M-CSF	Macrophage Colony Stimulating Factor
MCV	Mean Cell Volume

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
NK	Natural Killer Cells
NOAEL	No Observed Adverse Effect Level
NTM	Nontuberculous Mycobacteria
NTM-PD	Nontuberculous Mycobacterial Pulmonary Disease
NYHA	New York Heart Association
PCR	Polymerase Chain Reaction
PCV/EVF	Packed Cell Volume (PCV) Or Erythrocyte Volume Fraction (EVF) Also known as Hematocrit
PFT	Pulmonary Function Test
PT	Preferred Term
PT-INR	Prothrombin Time International Normalized Ratio
PVDS	Pharmacovigilance and Device Safety
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
ss	Subspecies
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Time of Maximum Plasma Concentration
UK	United Kingdom
USA	United States of America
WBC	White Blood Cells
WGS	Whole Genome Sequencing
ZN	Ziehl–Neelsen stain

5. INTRODUCTION

5.1. Background

Nontuberculous mycobacterial (NTM) infection

Pulmonary disease due to NTM is an increasing problem in the United States of America (USA) and most western countries. Over the last three decades an increasing incidence of pulmonary NTM isolation has been observed [Stout 2016, Wassilew 2016] and NTM are now recognized to be a major cause of chronic lung disease. Nontuberculous 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 prevalence ranging from 0.2 to 2.9 per 100,000 have been reported [Wassilew 2016] and across the USA prevalence ranges from 1 to 9 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 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 [Stout 2016,Wassilew 2016].

The cystic fibrosis (CF) population has an especially high risk for NTM infection and poses unique challenges with regards to diagnosis, treatment, and prevention [Floto 2016]. The reported prevalence of positive NTM cultures and/or NTM disease within various CF patient cohorts or at single centers varies dramatically but in the largest studies the overall prevalence is 6-13% [Adjemian 2014, Aitken 1993, Olivier 2003, Qvist 2014, Roux 2009, Sermet-Gaudelus 2003, Valenza 2008]. In a recent review of data from the CF Foundation Patient Registry, the median state prevalence of NTM in CF patients was 12% although this ranged from 0 to 28% [Adjemian 2014].

The overwhelming majority of NTM species recovered in CF samples in the USA are from either the *M. avium* complex (MAC) or the *M. abscessus* complex (MABSC) [Adjemian 2014]. Historically, MAC has been the most common NTM isolated, and in the largest USA survey it was present in up to 72% of patients with NTM-positive sputum cultures [Olivier 2003]. The percentage of MABSC reported in CF patients with NTM-positive sputum cultures has ranged from 18 to 64% [Olivier 2003, Pierre-Audigier 2005, Qvist 2014, Roux 2009, Seddon 2013 Sermet-Gaudelus 2003, Valenza 2008] and it does appear that the proportion of MABSC is

increasing with some centers reporting a greater frequency than MAC. In part, this effect may be due to geographic factors, as MABSC appears especially prevalent in Europe [Qvist 2014, Roux 2009, Sermet-Gaudelus 2003,Valenza 2008]. Differences in relative prevalence of MAC and MABSC may also relate to the age of the cohorts studied, as MAC is more often associated with older CF patients, often diagnosed in adulthood, while MABSC is frequently seen in younger patients and those with more severe lung disease [Catherinot 2013, Qvist 2014].

While MABSC is generally considered to be more virulent than MAC, in the setting of CF lung disease there are many examples where both of these microbes have been associated with fulminate disease. In the past several years, important distinctions between species within the MABSC have been defined. Clarithromycin exposure of *M. abscessus* subspecies (ss) *abscessus* strains typically induces resistance by day 7. In contrast, *M. abscessus* ss *massiliense* isolates nearly always remain susceptible to clarithromycin, as a result of a non-functioning *erm*(41) gene [Nash 2009]. This distinction appears to have considerable clinical significance, as in a recent study eradication was achieved in response to treatment in 88% of patients who grew *M. abscessus* ss *massiliense,* compared with only 25% ($p < 0.001$) in those with *M. abscessus* ss *abscessus* [Koh 2011]. It is possible that similar differences in virulence and treatment response exist between species and subspecies within MAC.

Historically, NTM infections have been attributed to environmental exposure [Bange 2001, Jonsson 2007, Sermet-Gaudelus 2003].

Recently, there have been reports of local outbreaks of *M. abscessus* ss *massiliense* within CF centers [Aitken 2012, Tettelin 2014] which suggests the potential for patient-to-patient transmission. In the Papworth CF Center, in the United Kingdom (UK), whole genome sequencing (WGS) as well as analysis of antibiotic resistance patterns identified two clustered outbreaks of *M. abscessus* ss *massiliense* [Bryant 2013]. Five patients who had overlapping clinical encounters at the University of Washington CF Center were found to have identical isolates of *M. abscessus* ss *massiliense* from the same genetic clade as the Papworth outbreak. Through WGS of the CF strains from the Seattle and Papworth outbreaks, as well as an outbreak of soft tissue infections in Brazil, research groups worldwide have found a very high-level of relatedness among these “transmissible strains”, when compared to a collection of worldwide strains [Tettelin 2014]. In CF patients, these transmissible strains appear especially virulent, with high mortality and treatment failure [Aitken 2012, Bryant 2013].

Successfully treating NTM disease is a major problem for clinicians and patients. Antibiotic options for NTM are poor [Griffith 2007, Griffith 2016]. The standard regimen for NTM (*M. avium*, *M. intracellulare* and *M. kansasii*) is a 3-drug regimen of a macrolide (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 [Aksamit 2017, Griffith 2007, Rawson 2016]. For this reason, the intention to treat cure rates in clinical trials are usually only 40-60% [Field 2004, Stout 2016, Xu 2014]. 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].

Clinical trials in NTM show microbiologic disease recurrence both during and following treatment. One study found that during therapy microbiologic disease occurred in 14% of patients (73% with reinfection MAC isolates, 27% with true relapse isolates: p = 0.03) and microbiologic recurrence occurred in 74 of 155 patients (48%) after completion of therapy (75% reinfection isolates, 25% true relapse isolates) [Wallace 2014]. 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]. Nontuberculous mycobacteria do progressively acquire drug-resistance, including to rifampicin, amikacin, macrolides and quinolones [Cowman 2016, Heidarieh 2016, Zhao 2014]. 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 *Escherichia 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 *Saccharomyces 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 characterized 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 (RBC) 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 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. The NOAELs from other toxicity studies than the 26-week study were 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 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 4 subjects in each of the three SAD dose levels (150 µg, 300 µg and 600 µg) and 6 subjects receiving placebo. In the MAD part, 24 subjects were included with 9 subjects in each of the two MAD dose levels (300 µg or 600 µg) and 6 subjects receiving placebo once daily for 6 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 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 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. A dose-dependent slight increase in heart rate was observed after dosing. There were no SAEs, severe AEs, dose-limiting toxicity, or other remarkable findings of clinical concern from review of clinical safety data.

The following clinical studies of inhaled molgramostim are ongoing:

- Study MOL-PAP-002 in subjects with autoimmune pulmonary alveolar proteinosis (aPAP)

  This pivotal clinical trial is ongoing in Australia, Europe, Israel, Japan, Russia, South Korea, Turkey, and the US. It is a randomized, double-blind, placebo-controlled trial, in which has enrolled 139 subjects 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 placebo daily. 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. Five reviews of unblinded safety data by an independent data safety monitoring board (DSMB) have been conducted, including 10, 38, 59, 96, and 134 randomized subjects, respectively. Data reviewed comprised AEs, safety laboratory data, vital signs and pulmonary function tests from up to 72 weeks of treatment. At all reviews the DSMB recommended that the trial could continue as planned.

- Study SAV006-03 in subjects with aPAP

  This is an open label, noncontrolled extension to MOL-PAP-002 to investigate safety of long term use of inhaled molgramostim (300 µg) administered intermittently in cycles of 7 days molgramostim, administered once daily, and 7 days off treatment for up to 3 years.

- Study SAV008-01 in non-CF subjects with NTM

  This pilot clinical trial is ongoing in Australia and the UK. It is an open-label, non-controlled, multicenter pilot trial, in which has enrolled 32 non-CF subjects with NTM infections. Treatment is given for 48 weeks and consists of daily administration of molgramostim nebulizer solution 300 µg. A safety data review was conducted after the first 6 subjects had completed 12 weeks of treatment. At this review the safety committee endorsed continuation of the trial and extension of the treatment duration from 24 to 48 weeks to increase the ability to observe a more robust anti-infective effect.

  An interim analysis was conducted after 14 subjects had completed 24 weeks of treatment. The interim analysis focused on safety and tolerability, assessed for all 32 subjects enrolled in the trial, and efficacy as assessed by microbiological results, in 14 subjects who completed the 24-week treatment period and had culture results available up to at least the 16-week timepoint. Ten of the evaluable subjects had MAC infection and four had MABSC infection. Of the subjects with MAC infection, eight were in treatment Group 1 (on anti-mycobacterial treatment) and two were in treatment Group 2 (not on anti-mycobacterial treatment). The four evaluable MABSC subjects were evenly split between both treatment groups.

  Summary of Microbiological Data

  The data showed that among the 10 subjects with MAC infection, four experienced a consistent sputum smear conversion to negative by week 24, and three experienced a negative sputum culture at weeks 16 and 20, with culture results pending for the week 24 timepoint. Sputum smear or sputum culture conversions were not observed in the four subjects with MABSC infection.

  Summary of Safety Information

  Among the 32 enrolled subjects, six (19%) experienced serious adverse events (SAEs), including one subject who died by suicide. The death was considered unrelated to treatment. One SAE was subsequently downgraded to a non-serious AE. The majority of SAEs consisted of hospitalizations due to pulmonary exacerbations or worsening of NTM infection, of which one was considered possibly treatment-related, i.e. one case of pulmonary exacerbation starting approximately 2.5 months after trial start. Molgramostim nebulizer solution was generally well tolerated, with nine subjects (28%) reporting mostly mild, potentially treatment-related respiratory adverse events (shortness of breath, chest tightness or wheeze) shortly after initiation of dosing. Respiratory adverse events were defined as shortness of breath, chest tightness or wheeze. A total of three subjects (9%) discontinued treatment due to adverse events, which were nausea and stomach pain, or shortness of breath. Two of these subjects subsequently restarted study drug on reduced dosage which was well tolerated.

  In line with its pharmacological effect as a stimulator of blood cells, molgramostim induced increased levels of eosinophils in blood in 17 subjects. The Investigators reported this as an asymptomatic finding, and a review of data did not identify a trend of decreased pulmonary function tests or respiratory adverse events associated with the

eosinophilia. The increase peaked at 4 weeks after start of treatment and levels decreased or plateaued at subsequent visits on continued treatment.

Subjects with CF were excluded from this study as, unlike the non-CF setting of NTM infection, these subjects typically have multiple pathogens identified at the time of NTM isolation.

5.2. 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% [Field 2004, Stout 2016, Xu 2014]. 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 (30–48%), especially in patients with nodular bronchiectatic lung disease [Lee 2015, Wallace 2014]. There is limited data on treatment outcomes in patients with CF and NTM infection. However, 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 or inability to tolerate the drug regimen. Response to further conventional NTM treatments in this group would be not expected. In addition, the potential of inhaled molgramostim to eradicate NTM infection in subjects who are not eligible for guideline-based antimycobacterial treatment due to lack of accelerated decline in pulmonary function or worsening of clinical symptoms beyond what is expected in CF will be explored. An increased risk of death has been shown with both NTM-PD (hazard ratio 1.63) and NTM isolation without pulmonary disease (hazard ratio 1.33) compared to matched controls [Marras 2013]. Thus, there is a rationale for treatment also of this group of patients.

Due to their thick cell wall and resistance to normal extracellular defense mechanisms, successful killing of mycobacteria requires phagocytosis by macrophages. 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 subjects 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 subjects 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 granulocytes, 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 [Bermudez 1994, Newman 1997, Onyeji 1995, Suzuki 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 including patients with CF with rhGM-CSF are also available. During the Acquired Immunodeficiency Syndrome (AIDS) epidemic, the administration of parenteral rhGM-CSF was reported to control systemic NTM infection resistant to antibiotic therapy and increase anti-mycobacterial activity [de Silva 2007, Hariadi 2017, Kemper 1998, Kedzierska 2000]. In addition a case of disseminated cutaneous MAC lesions refractory to conventional antimycobacterial therapy in a patient with chronic lymphocytic leukemia responded to the addition of subcutaneous GM-CSF and compounds that had recently been discovered to have anti-MAC activity (linezolid, mefloquine, moxifloxacin) [Nannini 2001]

There are also three case reports of patients with pulmonary diseases who have been successfully treated with GM-CSF. A 44 year old male with PAP and a partial response to repeated whole lung lavage was successfully treated with subcutaneous GM-CSF following discovery of *M. Kansasii* in the BAL fluid. Several cavitating lesions were apparent on his chest radiographs and CT scan. He was initially treated with isoniazid, rifampicin and ethambutanol for 12-18 months which was subsequently switched to rifabutin, clarithrimycin and ethambutol until he underwent another set of BAL to relieve his breathlessness. Two months later a chest radiograph showed a recurrence of the pulmonary infiltrates so after a fourth set of BAL he commenced GM-CSF for 3 months to prevent recurrence. The patient was reported as remaing well for more than 6 months since GM-CSF treatment stopped [AbdulRahman 2004].

Two cases of adult patients with CF 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]. A recent publication also details the successful treatment of two CF patients with

evidence of M. abscessus colonization who were experiencing a decline in pulmonary function and clinical stability with inhaled GM-CSF [Scott 2018]. The first patient (a 10-year-old delta F508 homozygous female) had a 3.5-year history of persistent M. abscessus colonization. The patient had lack of response to aminoglycosides and/or linezolid. Aerosolized rhGM-CSF was added and administered on alternate weeks. Clinical improvement and stability were noted without toxicity. GM-CSF was continued, and antibiotics were discontinued after 3 months. After remaining off antibiotics for 3 months a decision was made to recombine aerosolized GM-CSF with linezolid (IV) and amikacin (inhaled). After 4 months of combined therapy both acid-fast bacilli smear and cultures became negative. The patient remains on inhaled GM-CSF alone. Over 90 weeks, her FEV_1 increased from 64.7 to 78.0 percent predicted. The second patient (a 25-year-old delta F508 homozygous male) had a 13-year history of persistent M. abscessus colonization, which was not treated with antibiotics. When the clinical status worsened (weight loss, decreased pulmonary function tests, and new radiological infiltrates), aerosolized GM-CSF treatment was administered on alternate weeks without antibiotic therapy. Clinical improvement was noted without toxicity. After 6 months of GM-CSF sputum smears became negative and culture burden decreased to 1 colony per plate. His FEV_1 increased from 55.2 to 63.9 percent predicted.

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 it is well tolerated. In animal studies as well as in the human Phase I study there was no increase in airways reactivity and in the Phase I study there was no anti-drug antibody development. The interim data from trial SAV008-01 indicate that some subjects may experience respiratory adverse events such as shortness of breath, chest tightness and wheeze, mainly mild and reversible, after initiation of dosing. In case of symptoms of bronchoconstriction or drop in FEV1 by 15 % or more, a short-acting bronchodilator should be administered 10-45 minutes prior to each subsequent dosing in the trial.

Furthermore, in accordance with the pharmacological effect of molgramostim, increased levels of eosinophils in blood was observed in 17 subjects in trial SAV008-01. A review of data did not identify a trend of decreased pulmonary function tests or respiratory adverse events associated with the eosinophilia. In the current trial, white blood cells and differentials will be monitored before and 2 hours after dosing at selected visits to further characterize this effect.

In the phase I trial in healthy volunteers a dose-dependent slight increase in heart rate was observed after dosing. Subjects with CHF NYHA Class III or IV and those with a recent ischemic heart event will therefore be excluded. Vital signs will be repeated 2 hours after dosing at selected visits.

Clinical experience in using inhaled molgramostim in the setting of alveolar proteinosis has so far shown the drug to be well tolerated with few adverse drug reactions reported in the more than 100 subjects 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 subjects in the setting of alveolar proteinosis.

In the current study, the subject population is adult CF subjects with persistent pulmonary NTM infection as evidenced by at least three positive sputum cultures in the prior 2 years, one of

which has to be within 6 months prior to Screening, and a positive culture within 10 weeks prior to Baseline. Within the CF population, subjects with NTM disease can have sporadic negative cultures, and thus subjects will be allowed to rescreen if known to have NTM disease but were found to have a negative culture at the time of Screening. A population of treatment-resistant or treatment-intolerant subjects was selected as these are the subjects 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 or could not tolerate treatment) subjects will be stratified into Group 1 and Group 2 as follows. In addition, subjects without signs of NTM-PD but who still might benefit from a potential eradication of NTM infection will be recruited into a third group.

- Group 1: Subjects with chronic pulmonary MAC or MABSC infection who have not consistently achieved negative NTM sputum cultures while currently on a multidrug NTM guideline-based antimycobacterial regimen, which has been ongoing for at least 9 months prior to the Baseline visit.
- Group 2: Subjects with chronic pulmonary MAC or MABSC infection 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.
- Group 3: Subjects with chronic -pulmonary MAC or MABSC infection not meeting recommendations for treatment with a multidrug NTM guideline-based antimycobacterial regimen based on failure to meet ATS/IDSA criteria for NTM pulmonary disease (i.e. absence of radiologic findings and clinical symptoms beyond what is expected from underlying CF).

In this trial, molgramostim 300 µg once daily will be administered for 48 weeks via inhalation using the Investigational eFlow Nebulizer System (PARI Pharma GmbH, Germany). The same dose and regimen are being investigated over a 48-week treatment period in the pilot clinical trial of inhaled molgramostim in non-CF subjects with persistent pulmonary NTM infection (Study SAV008-01) and for 24 weeks in the pivotal clinical trial in aPAP (MOL-PAP-002). In the current trial the treatment duration was set to 48 weeks as prolonged treatment is generally required when treating NTM in CF subjects with antimycobacterials, and the published case report of inhaled GM-CSF indicate that treatment beyond 6 months may be beneficial [Scott 2018].

A data review will be conducted after the first 6 subjects have completed 12 weeks of treatment. If safety concerns or poor tolerability are identified in this review, the review committee may decide on less frequent dosing for subsequent subjects in the study. Additional safety reviews will be conducted at regular intervals thereafter.

5.3. 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, NTM-PD 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.

As the majority of inhalational use of rhGM-CSF has been in the context of aPAP, where subjects 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. Based on previous trials, these effects may include respiratory adverse events, eosinophilia and a slight increase in heart rate. 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 will be conducted by a review committee (the lead Investigators and sponsor representatives) after the first 6 subjects have completed 12 weeks treatment as outlined above. This may result in reduced dosing frequency if there are safety concerns or poor tolerability. Recruitment beyond the 6 first subjects will not be stopped during the review period. Additional safety reviews will be conducted at regular intervals thereafter. 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.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective is:

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

6.2. 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 pulmonary function.
- To investigate efficacy of inhaled molgramostim on patient reported outcomes.
- To investigate efficacy of inhaled molgramostim on BMI.
- To investigate safety of inhaled molgramostim in subjects with NTM infection.

6.3. Exploratory Objectives

The exploratory objectives are:

- To investigate efficacy in subjects infected with MABSC and MAC, respectively.
- To investigate efficacy in subjects on concurrent anti-mycobacterial treatment and subjects not on anti-mycobacterial treatment, respectively.
- To investigate rates of recurrence and reinfection after End of treatment.
- To investigate efficacy of inhaled molgramostim on bacterial co-infections.
- To investigate efficacy of inhaled molgramostim on frequency of pulmonary exacerbations
- To investigate efficacy of inhaled molgramostim on morphologic findings on CT scans of the lung.

6.4. Endpoints

6.4.1. Efficacy Endpoints

6.4.1.1. Primary Efficacy Endpoint:

- Number of subjects with NTM sputum culture conversion to negative (defined as at least three consecutive negative mycobacterial cultures collected at least 4 weeks apart during the Treatment period).

6.4.1.2. Secondary Efficacy Endpoints:

- NTM sputum culture microbiological cure (defined as multiple consecutive negative but no positive cultures with the causative species after last culture conversion and until the End of Treatment (Week 48)).
- Time to first NTM sputum culture conversion during the Treatment period.
- Sputum smear conversion to negative (defined as at least three consecutive negative AFB stained sputum smears on microscopy, collected at least 4 weeks apart in subjects who were smear positive at Baseline) during the Treatment period.
- Consistent sputum smear conversion to negative (defined as multiple consecutive negative but no positive smears after last smear conversion and until the End of Treatment (Week 48) in subjects who were smear positive at Baseline).
- Time to first NTM sputum smear conversion during the Treatment period.
- Durable NTM sputum microbiological cure for the NTM isolate(s) treated without recurrence at Week 12 after End of Treatment.
- Durable NTM sputum smear conversion to negative without subsequent positive smears at Week 12 after End of Treatment.
- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to End of Treatment and Week 12 after End of Treatment.
- Absolute change in FEV1 (percent predicted) from Baseline to End of Treatment and Week 12 after End of Treatment.
- Change in respiratory domain score assessed by CFQ-R from Baseline to End of Treatment and Week 12 after End of Treatment.
- Change in BMI from Baseline to End of Treatment and Week 12 after End of Treatment.

6.4.1.3. Exploratory Endpoints:

- Change from Baseline in time to positivity on NTM liquid culture media at Treatment visits and Follow-up.
- Change in semi-quantitative grade of sputum cultures from Baseline to Treatment visits and Follow-up.

- Number of subjects with recurrence (re-emergence of the treated NTM species after End of Treatment), or reinfection (emergence of a different NTM species, after End of Treatment).
- Eradication and/or reduction in bacterial load of co-infections in sputum.
- Frequency of pulmonary exacerbations compared to the previous year.
- Change in CFQ-R domains scores for physical functioning, vitality, health perceptions, treatment burden, role functioning, emotional functioning, and social functioning.
- Change in CT scans from Baseline to End of Treatment (Week 48).

6.4.2. Safety Endpoints

- Number of AEs, SAEs, ADRs, severe AEs and AEs leading to treatment discontinuation during the trial period.
- Change in WBC counts and differentials in blood from Baseline to Treatment visits.
- A clinically significant decrease in FEV_1 (% predicted) from Baseline to Treatment visits that does not respond to typical CF treatment (including treatment of pulmonary exacerbation if suspected) and in the judgement of the Investigator is not due to typical complication of CF (*i.e*. acute pulmonary exacerbation).
- GM-CSF levels during Treatment period.
- Development of anti-drug antibodies during Treatment period and Follow-up period.

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design

This is an open-label, non-controlled, multicenter, pilot clinical trial of inhaled molgramostim in CF subjects with NTM infections. The study will include up to 34 subjects.

The primary objective is to investigate efficacy of inhaled molgramostim on NTM sputum culture conversion to negative. The primary endpoint is NTM sputum culture conversion to negative (defined as at least three consecutive negative mycobacterial cultures collected at least 4 weeks apart during the Treatment period).

Secondary objectives include investigation of the efficacy of inhaled molgramostim on NTM sputum smear conversion to negative, reduction of NTM bacterial load in sputum, pulmonary function, Patient Reported Outcomes, and BMI as well as evaluation of the safety of inhaled molgramostim in these subjects. Secondary efficacy endpoints and the safety endpoints are detailed in Section 6.4.

The Screening period will begin up to 10 weeks prior to the Baseline visit for collection of the sputum sample, but the remainder of the assessments including Safety labs will be completed within 6 weeks of Baseline, to determine eligibility. Adult subjects with a history of CF and chronic pulmonary NTM infection will be considered for enrollment. Chronic pulmonary NTM infection will be defined by at least three positive NTM cultures (sputum or BAL) for the same species/subspecies of MAC or MABSC within the 2 years prior to screening, with at least one positive within the past 6 months prior to screening and a minimum of 50% of NTM cultures positive over the past 2 years. Subjects must additionally provide - a positive sputum culture with the same species/subspecies from the central laboratory at Screening to be eligible. The Screening sample may be collected up to 10 weeks prior to Baseline, provided informed consent is signed. Subjects who have a negative sputum culture at the time of Screening will be allowed to rescreen.

Three groups of subjects will be recruited:

- Group 1: Subjects with chronic pulmonary MAC or MABSC infection who have not consistently achieved negative NTM sputum cultures while currently on a multidrug NTM guideline-based antimycobacterial regimen, which has been ongoing for at least 9 months prior to the Baseline visit.
- Group 2: Subjects with chronic pulmonary MAC or MABSC infection 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.
- Group 3: Subjects with chronic pulmonary MAC or MABSC infection not meeting recommendations for treatment with a multidrug NTM guideline-based antimycobacterial regimen based on failure to meet ATS/IDSA criteria for NTM pulmonary disease (i.e. absence of radiologic findings and clinical symptoms beyond what is expected from underlying CF).

All subjects will have a Screening, Baseline, Week 1 and 2, followed by monthly visits from week 4 during the Treatment period. The Treatment period will be 48 weeks. Following the End of Treatment, subjects will have a Follow-up visit at 4 and 12 weeks, and the End of Study visit 24 weeks after the End of Treatment.

Subjects on a cyclical on-off anti-Pseudomonal regimen will have their trial visits (Baseline and subsequent visits in the Treatment Period) scheduled during a week after at least three weeks off-treatment or after at least one week on-treatment of the antibiotic. Subjects on a continuous inhaled regimen, including CAT, should have been on a stable regimen for at least 28 days prior to Baseline.

At the Baseline visit, eligible subjects will start treatment with inhaled molgramostim.

At Screening, Baseline, each monthly visit during the Treatment Period, and all Follow-up visits, sputum samples for staining and microscopy, and microbiological culture will be collected. If required, induced sputum may be obtained according to local practice. At Screening, Baseline, and all monthly visits during the treatment period and all follow up visits, subjects will be asked to collect two samples at home, preferably on the consecutive days after the site visit but within 5 days of the visit.

At Baseline, and subsequent visits, clinical assessments including body weight, vital signs, patient reported outcomes (CFQ-R), and PFTs to include FEV_1, FVC and FEV_1/FVC will be conducted (according to Table 1). A low-dose CT scan or CT Scan performed to institutional standard of care will be conducted at Baseline and at End of Treatment. In case of a clinically significant drop in FEV_1 not responding to standard CF care the CT scan may be repeated. Safety assessments will include FEV_1, ECG, safety laboratory assessments, serum anti-drug antibodies and GM-CSF levels. At Screening, Baseline, and monthly visits in the Treatment Period and at the 4-week Follow-up visit a pregnancy test/contraceptive check will be conducted. At each visit any changes in concomitant medication will be recorded. Participating subjects will be encouraged to contact the clinic between visits if they experience AEs, worsening of their condition or have any other concerns. If needed, unscheduled visits will be conducted at Investigator's discretion.

All subjects will be maintained on their standard CF treatment and medications independent of NTM treatment status.

During the study, subjects in Group 1 will continue use of antimycobacterial treatment whereas Groups 2 and 3 will receive inhaled molgramostim as monotherapy for their NTM infection. For subjects in Group 1, the antimycobacterial therapy should preferably not change during the treatment period except in case of drug toxicity or adverse reactions. Antibiotics discontinued due to toxicity may be replaced, with drug selection and dose modification at the discretion of the treating physician. All changes in antimycobacterial treatment will be recorded, including reasons for each change. In the event the Investigator has evidence of infection while on treatment which requires more intensive therapy (i.e. additional antibiotics in Group 1 or addition of antibiotics to Group 2 or 3) the subject may be allowed to continue after discussion with the Sponsor medical monitor.

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 administered via the Investigational eFlow Nebulizer System. Dosing will be done in the morning, after completion of the subject's normal airway clearance routine, and inhaled antibiotics. A data review will be conducted after the first 6 subjects have completed 12 weeks of treatment. If safety concerns or poor tolerability are identified in this review, the review committee may decide on less frequent dosing for subsequent subjects in the study. Any changes to the conduct of the study such as change of dose, dose regimen or duration will be documented in a protocol amendment. Additional safety reviews will be conducted at regular intervals thereafter.

7.1.1. Trial Period

The duration of trial participation for each subject is approximately 73 to 82 weeks:

- Screening period for the subjects is 1 to 10 weeks
- Treatment period is 48 weeks (+/- 7 days)
- Follow-up for 24 weeks (+/- 7 days)

7.1.2. End of Trial

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

7.1.3. Trial Completion

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

7.2. Number of Subjects

A minimum of 30 subjects will be enrolled. No formal sample size calculation was done as this is an initial pilot study. To be able to assess response in each of the three groups, a minimum of 8 subjects with MAC or MABSC will be enrolled in each group, and a minimum of 30 subjects will be enrolled across all 3 groups. The maximum number of subjects enrolled into each group will be 12, and the maximum number of subjects enrolled into the study will be 34.

Table 3. Number of Subjects

Organism	**Group 1**	**Group 2**	**Group 3**	**Total**
MAC/MABSC	8-12	8-12	8-12	30-34

7.3. 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.

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

system. Subjects successfully assigned to one of the treatment groups will then start treatment with open-label molgramostim nebulizer solution.

7.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to be captured in the eCRF. Minimal information includes informed consent and demography, eligibility criteria, screen failure details, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened upon approval from Sponsor. Rescreened subjects will be assigned a new site-specific subject number.

7.5. Dose Adjustment Criteria

7.5.1. Safety Criteria for Adjustment or Stopping Doses

There are no prespecified dose adjustment criteria.

A data review will be conducted by a safety review committee comprised of the lead Investigators and sponsor representatives after the first 6 subjects have completed 12 weeks of treatment. If safety concerns or poor tolerability are identified in this review, the review committee may decide on less frequent dosing for subsequent subjects in the study. Additional safety reviews will be conducted at regular intervals thereafter.

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. The Sponsor medical monitor should be consulted prior to dose reduction.

7.5.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

7.6. Criteria for Study Termination

The Investigator or the sponsor may terminate this trial prematurely for any reasonable cause. The 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.

8. 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.

8.1. Subject Inclusion Criteria

1. Written informed consent obtained from participant.
2. Confirmed diagnosis of CF according to the CFF 2017 Consensus Guidelines.
3. History of chronic pulmonary infection with MAC or MABSC (defined as at least three positive NTM cultures (sputum or BAL) for the same species (MAC) or subspecies (MABSC) within the 2 years prior to screening, with at least one positive within the 6 months prior to screening, and a minimum of 50% of NTM cultures positive over the past 2 years) that does not demonstrate response to current treatment course based on decreasing NTM burden or frequency of positive cultures, and in the opinion of the Investigator is unlikely to resolve with current treatment course.
4. Subject fulfills criteria for inclusion in one of the following groups:
    - Group 1: Subject with chronic pulmonary MAC or MABSC infection currently on a multidrug NTM guideline-based antimycobacterial regimen, which has been ongoing for at least 9 months prior to the Baseline visit.
    - Group 2: Subject with chronic pulmonary MAC or MABSC infection who has stopped a multidrug NTM guideline-based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance.
    - Group 3: Subject with chronic pulmonary MAC or MABSC infection not meeting recommendations for treatment with a multidrug NTM guideline-based antimycobacterial regimen based on failure to meet ATS/IDSA criteria for NTM pulmonary disease (i.e. absence of radiologic findings and clinical symptoms beyond what is expected from underlying CF).
5. Ability to produce sputum or be willing to undergo an induction that produces sputum for clinical evaluation.
6. An additional sputum culture performed by central laboratory, which is positive for the same species (MAC) or subspecies (MABSC) of NTM as before the trial within 10 weeks of Baseline.
7. CF which in the Investigator's opinion is clinically stable and is not expected to require lung transplantation within the next year.
8. $FEV_1 \geq 30\%$ of predicted at screening that is normalized for age, gender, race, and height, using the Global Lung Function Initiative (GLI) equation.
9. Subjects who are co-infected with a respiratory pathogen, e.g. *P. aeruginosa or S. aureus*, must either be stable on a regular suppression antibiotic regimen or must be, in the opinion of the Investigator, stable despite the lack of such treatment.

10. Female or male ≥18 years of age.
11. If female, subjects 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) during and until 30 days after last dose of trial treatment, having 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.

    For purposes of this study, the Sponsor defines "acceptable methods of contraception" as:

    - Oral birth control pills administered for at least 1 monthly cycle prior to administration of the study drug.
    - A synthetic progestin implanted rod (eg, Implanon®) for at least 1 monthly cycle prior to the study drug administration but not beyond the 4th successive year following insertion.
    - Intrauterine devices (IUDs), inserted by a qualified clinician for at least 1 monthly cycle prior to study drug administration.
    - Medroxyprogesterone acetate (eg, Depo-Provera®) administered for a minimum of 1 monthly cycle prior to administration of the study drug and continuing through 1 month following study completion.
    - Hysterectomy or surgical sterilization.
    - Vasectomized partner
    - Abstinence.

    Double barrier method (diaphragm with spermicidal gel or condoms with contraceptive foam) is not considered an acceptable from of contraception.

    NOTE: For subjects prescribed Orkambi: Orkambi may substantially decrease hormonal contraceptive exposure, reducing the effectiveness and increasing the incidence of menstruation-associated adverse reactions. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.
12. If male, subjects who, if sexually active of reproductive potential and non-sterile (i.e., male who has not been sterilized by vasectomy for at least 6 months, and not diagnosed with infertility through demonstration of azoospermia in a semen sample and/or absence of vas deferens through ultrasound) are willing to use a barrier method of contraception, or their female partner must use an acceptable method of contraception, during the study and until 30 days after last dose of medication.
13. 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.

8.2. Subject Exclusion Criteria

1. Use of non-maintenance antibiotic for a pulmonary or extrapulmonary concurrent infection within 28 days prior to the Baseline visit.
2. Use of a maintenance antibiotic regimen containing azithromycin for a concurrent non-NTM pulmonary infection within 28 days prior to the Baseline visit. For subjects in Group 1, azithromycin is allowed if part of an ongoing multidrug NTM guideline-based antimycobacterial regimen.
3. Prior therapy with inhaled or systemic GM-CSF.
4. Subjects with hemoptysis of ≥60 mL in a 24-hour period within 4 weeks prior to Screening.
5. Life expectancy of less than 6 months according to Investigator's judgement.
6. History of, or present, myeloproliferative disease, leukemia or other hematological malignancy.
7. Active pulmonary malignancy (primary or metastatic); or any malignancy requiring chemotherapy or radiation therapy within 1 year prior to Screening or anticipated during the study period.
8. Active autoimmune disorder or other condition requiring therapy with significant immunosuppression, e.g. such as corticosteroids at a dose equivalent of 10 mg/day or more of prednisolone, or other immunosuppressant medications, within 3 months prior to Screening or anticipated during the study period. Inhaled or topical corticosteroids, or brief courses (< 14 days) of systemic corticosteroids for pulmonary exacerbations or other self-limited conditions are permitted.
9. Changes in antimicrobial, bronchodilator, anti-inflammatory or corticosteroid medications, or changes in CFTR modulators, within 28 days prior to the Baseline visit.
10. Pulmonary tuberculosis requiring treatment or treated within 2 years prior to Screening.
11. History of human immunodeficiency virus (HIV) infection or other disease associated with significant immunodeficiency.
12. History of lung or other solid organ transplantation or currently on the list to receive lung or other solid organ transplantation.
13. History of congestive heart failure (CHF) New York Heart Association (NYHA) Class III or greater in severity.
14. History of cardiovascular ischemic event within 6 months of Baseline.
15. Any change in chronic NTM multi-drug antimycobacterial regimen within 28 days prior to Screening.
16. Treatment with any investigational medicinal product within 28 days of Screening.
17. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product.

18. Any other condition that, in the opinion of the Investigator, would preclude informed consent or assent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

8.3. Subject Withdrawal Criteria

8.3.1. 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 and attend the remaining visits.

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

8.3.2. 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 AE
- 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 11.14.

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.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Table 4: Investigational Product

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

9.2. Prohibited Medications

The following **concomitant medications are not allowed during the trial** (See exclusion criteria Section 8.2):

- Treatment with azithromycin for a concurrent pulmonary infection. Note: For subjects in Group 1, azithromycin is allowed as part of an ongoing multidrug NTM guideline-based antimycobacterial regimen.
- Treatment with other inhaled or systemic GM-CSF.
- Therapy associated with significant immunosuppression such as e.g. systemic prednisolone at a dose equivalent of 10 mg/day or more.

Inhaled or topical corticosteroids, or brief courses (< 14 days) of systemic corticosteroids for pulmonary exacerbations or other self-limited conditions are permitted. The Medical Monitor should be consulted if systemic corticosteroids at a dose equivalent of 10mg/day or more are expected to last more than 14 days for a pulmonary exacerbation or self-limited condition.

9.3. 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.

9.4. Randomization and Blinding

Not applicable.

9.5. 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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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

10.2. 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 4 weeks will be supplied in adequate amounts at the dispensing visits.

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

10.3. 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, 28, 32, 36, 40, and 44 (Visits 5-15) during the Treatment period.

Subjects will be instructed to store the kit at 2-8°C in a safe and secure place away from sunlight and out of the reach of children. The IMP must not be frozen or shaken and not be used beyond the expiration date on the vial. The IMP should be removed from refrigeration 10 minutes prior inhalation.

Subjects will be asked to return used and unused medication at the next clinic visit to check compliance. At Weeks 1 and 2 (Visits 3 and 4) subjects will be asked to bring their used IMP and one unused IMP dose with them to the clinic.

10.4. Study Drug Preparation

Not applicable.

10.5. Administration

The Investigational eFlow Nebulizer System (PARI Pharma GmbH, Germany) will be used to administer the IMP. The eFlow Nebulizer 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 (maximum fill 4 mL) that can produce aerosols with high density of active drug, precisely defined droplet size (mass median diameter 2.9-3.9 µm) 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 take place at the Baseline visit and will be checked at subsequent clinic visits. The subjects will also receive written instructions.

The subjects will administer the first dose of IMP at the Baseline visit (Visit 2) and subsequent visits in the Treatment period under the supervision of trial personnel.

When administering as part of the morning routine at home, the following order should be applied: bronchodilator, dornase alfa (Pulmozyme), inhaled antibiotics such as TOBI, and lastly IMP.

10.6. 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.

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.

10.7. Study Drug Handling and Disposal

Used and Unused IMP must be returned to supply vendor after agreement with the Sponsor, but only after drug accountability has been completed by the CRA. 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.

11. ASSESSMENTS

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

11.1. 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, including 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 consent form. Information provided to a subject can be delegated to a qualified member of the research team, but the Investigator must be available for questions and this should be documented in source documents..

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 informed consent form will be updated by Savara and approved by an IRB. The subject must be informed in a timely manner about the updated information and written informed consent must be obtained.

11.2. 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 Table 1 .

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

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

At all visits other than Visit 3 and 4 subjects will be asked to collect two additional morning sputum samples at home on different days preferably on consecutive days after the site visit but within 5 days of the site visit. On dosing days, the samples should be collected prior to the dosing of trial drug.

Additional samples for NTM testing may be collected between visits according to Investigator's discretion and will then be recorded as an unscheduled visit.

The sputum samples must be refrigerated immediately after sampling unless being shipped to the central laboratory on the same date. Details regarding the collection and handling of sputum samples will be provided in a separate document.

Using AFB staining (fluorescence and /or ZN stain) NTM in sputum will be identified and a semi-quantitative assessment of bacterial load (graded as 0, scant, 1+, 2+, 3+) will be conducted.

Microbiological culture to identify growth of NTM will be conducted using established standards. A semi-quantitative assessment of sputum cultures will be reported. Identification to NTM species level (MAC) or subspecies level (MABSC) will be conducted on positive samples (one per visit) using established methods. Isolates from selected samples may also be subject to molecular identification to the subspecies level, and whole genome sequencing to track potential polyclonal infections and/or new acquisition of NTM infection during the follow-up period at the central laboratory, according to a separate research protocol. These data may be reported outside the CTR.

If sufficient sputum volume is obtained, an additional aliquot may be frozen and stored for potential post-hoc analysis by quantitative polymerase chain reaction (PCR). Such PCR analysis will be performed no later than 2 years after trial completion. The PCR data will not be included in the CTR but reported separately.

Routine CF bacteriology and fungal cultures will be performed locally on the sputum sample collected at the site. Semiquantitative assessment of bacterial load will be done for pathogens according to clinical standard.

11.3. 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 all antimycobacterials taken for the current NTM infection within 2 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.

Treatments for cystic fibrosis, including inhaled antibiotics and CFTR modulators, should have been used in a stable regimen for at least 28 days prior to Baseline.

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.

If new antibiotics are prescribed for a concurrent infection, it will be assessed to determine whether the reason for the antibiotic therapy is a pulmonary exacerbation. All exacerbations must be reported as AEs.

Antimycobacterial therapy should preferably not change during the treatment period except in case of toxicity or adverse reactions. For subjects in Group 1, the antimycobacterial therapy should preferably not change during the treatment period except in case of drug toxicity or adverse reactions. Antibiotics discontinued due to toxicity may be replaced, with drug selection

and dose modification at the discretion of the treating physician. In the event the Investigator has evidence of infection while on treatment which requires more intensive therapy (i.e. additional antibiotics in Group 1 or addition of antibiotics to Group 2 or 3) the subject may be allowed to continue after discussion with the Sponsor medical monitor.

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.

11.4. Patient Reported Outcomes

The patient reported outcome (CFQ-R) will be assessed at the timepoints shown in Table 1.

The CFQ-R is a disease-specific health-related quality of life measure for patients with CF with a two-week recall period. The CFQ-R measures functioning in a variety of domains, including Physical Functioning, Vitality, Health Perceptions, Respiratory Symptoms, Treatment Burden, Role Functioning, Emotional Functioning, and Social Functioning. The CFQ-R should be conducted prior to any other study visit procedure. A sample of the questionnaire is presented in Appendix 2.

11.5. 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. For the week 1 (Visit 3) and Week 2 (Visit 4) the subject will be asked to bring the diary back to the site for review by the study staff. At all other visits during the treatment period the subject will return their diary to the study staff.

11.6. Adverse Events

Any AEs will be reported at every visit from Baseline (Visit 2) to the completion of the 24-week follow-up (Visit 19). Subjects will be encouraged to contact the clinic in between visits if they experience AEs or have any concerns. SAEs will be captured from the time the informed consent has been signed, up the last visit. For further information of definitions and reporting of AEs and SAEs, see Section 11.14.

11.7. Demographics/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/Alaska Native/Native Hawaiian/Other Pacific Islander)
- Smoking (Previous/Current/Never)
- Relevant prior and concurrent disorders, including other pertinent respiratory history such as number of pulmonary exacerbations within the last year and dates, all concurrent and relevant prior respiratory infections, and other CF related co-morbidities.
- Details of NTM history, such as results from all NTM cultures obtained during the last 2 years, will be recorded. If the participant has ever been treated for NTM previously, the species treated, and year treatment ended will be recorded.

11.8. 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 focusing on lungs may be performed as clinically indicated. New abnormal clinically significant physical examination findings not present during the Baseline visit should be recorded as AEs and followed during subsequent visits.

11.9. 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
- Body temperature (°C)

At selected visits as shown in Table 1, vital signs will be repeated approximately 2hours after dosing.

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

11.10. 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, QT and QTc 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.

11.11. Radiology

11.11.1. CT Scan

A low dose CT scan or CT scan using institutional standard of care of the lung will be performed at Baseline and the End of Treatment visit (Table 1). In case of a clinically significant drop in FEV_1 not responding to standard CF care, the CT scan of the lung may be repeated. The same type of CT scan (i.e. either low- or high- dose CT scan) should preferably be used at the Baseline and the End of Treatment visits to the extent feasible according to local institutional standard of care. Images will be uploaded into the eCRF and a standardized system for central scoring will be implemented at a later timepoint. If a chest radiograph is done information on the results will be collected in the eCRF.

11.12. Pulmonary Function Tests

11.12.1. Spirometry

All subjects will undergo standardized pulmonary function testing as shown in Table 1 by site staff with documented training in PFTs. Assessments will include FEV_1, FVC and FEV_1/FVC and be done in accordance with American Thoracic Society (ATS) guidelines (2005). Subjects will be tested using the same spirometry equipment provided by the Sponsor. Up to 8 efforts should be performed to obtain 3 acceptable and reproducible test results. The results will be uploaded and read centrally.

At Baseline (Visit 2) PFTs will be conducted before and 1.5 hours (+/- 30 minutes) after dosing of IMP. At all other dosing visits PFTs should be done 1.5 hours (+/- 30 minutes) after dosing. If there are symptoms of bronchoconstriction after inhalation of study drug at any time during the study, or if FEV_1 drops by 15% or more after dosing, a short-acting bronchodilator (e.g. 2 puffs of albuterol) may be prescribed at the investigators discretion for use 10-45 minutes prior to inhalation of study drug for the remainder of the treatment period.

Participants who routinely use bronchodilators should use them consistently throughout the study. Standard guidelines are noted below as a reference:

- Participants who routinely use short acting inhaled bronchodilators should use them 15 minutes to 2 hours prior to PFTs.
- Participants who routinely use long acting bronchodilator agents should use them 15 minutes to 6 hours prior to PFTs.

11.13. 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 325 mL with a maximum of 30 mL for one visit.

11.13.1. Levels of GM-CSF and Anti-GM-CSF Antibodies

Blood samples for assessment of GM-CSF and anti-GM-CSF antibodies will be taken prior to dosing at the clinic visit at the timepoints shown in Table 1. An additional blood sample for assessment of GM-CSF will be taken approximately 2 hours post dose.

Analyses will be performed at a central laboratory. If neutralizing antibodies to GM-CSF are identified, additional analyses exploring GM-CSF signaling may be done on a stored sample at a specialized laboratory.

11.13.2. Laboratory Safety Assessments

Blood samples for laboratory safety assessment should be taken prior to dosing at the clinic visit. At selected visits as shown in Table 1, sampling for analysis of WBC count and differentials will be repeated approximately 2 hours after dosing.

The laboratory safety analyses (hematology, clinical chemistry and urinalysis) will be performed by a central laboratory.

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’.

11.13.2.1. Blood Hematology

The following parameters will be analyzed:

Hemoglobin, RBC count, red blood cell distribution width (RDW), hematocrit (PCV/EVF), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelet count, WBC count, and white cell differential absolute count: neutrophils, lymphocytes, monocytes, eosinophils, basophils, and prothrombin time international normalized ratio (PT-INR).

11.13.2.2. Blood Chemistry

The following parameters will be analyzed:

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase, amylase, bilirubin, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), creatine phosphokinase (CPK), potassium, sodium, calcium, chloride, bicarbonate, phosphate, magnesium, total protein, albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and glucose (non-fasting).

11.13.2.3. Urinalysis

The following parameters will be analyzed:

pH, specific gravity, bilirubin, glucose, ketones, RBCs, WBCs, protein, microalbuminuria, and microscopic elements.

11.13.2.4. Pregnancy Screen

A serum pregnancy test and contraceptive check will be performed for female subjects at the timepoints 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.

11.14. Adverse and Serious Adverse Events

11.14.1. Definition of Adverse Events

11.14.1.1. 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.

11.14.1.2. Serious Adverse Event (SAE)

Any untoward medical 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 subject 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).

11.14.1.3. 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.

11.15. 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 24-week follow-up visit (Visit 19). 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.

11.16. Reporting Adverse Events

11.16.1. 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. Any SAEs occurring to a subject after the subject 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 IRB (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 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 IRB, 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 Pharmacovigilance as soon as possible. All 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 subject, the Investigator has to provide any additional information necessary as requested by the sponsor, the competent authorities concerned and ethics committees concerned.

11.16.2. SUSAR Reporting Procedure

The FDA and/or other applicable Regulatory Authorities and all participating Investigators will be notified by a written Investigational New Drug Application (IND) safety report and/or other applicable regulatory report (eg, expedited case report) of any suspected adverse reaction that is both serious and unexpected (i.e. a SUSAR), no later than 15 calendar days from the “date learned” of the event. In addition, all applicable regulatory bodies will be notified within 7 calendar days of any unexpected fatal or life-threatening suspected adverse reaction.

An untoward and unintended response to a non-study drug is, by definition, not a SUSAR.

11.16.3. Adverse Events of Special Interest

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

11.16.4. Precautions/Overdose

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/or neutrophilia may occur in case of systemic exposure. With high doses of similar products administered systemically, 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.

11.16.5. 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 11.16.1. 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.

11.16.6. 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 subjects from immediate risks.

12. STATISTICS

A minimum of 30 subjects will be enrolled. No formal sample size calculation was done as this is an initial pilot study. To be able to assess response in each of the three groups, a minimum of 8 subjects with MAC or MABSC will be enrolled in each group, and a minimum of 30 subjects will be enrolled across all 3 groups. The maximum number of subjects enrolled into each group will be 12, and the maximum number of subjects enrolled into the study will be 34

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 (SAP).

12.1. Efficacy Endpoints

Each group (Group 1, Group 2 and Group 3) will be analyzed separately. Data will be presented descriptively and using 95% CIs. Statistical summaries comparing post-treatment values with Baseline will be conducted for selected endpoints. For the time until sputum culture and smear conversion, Kaplan-Meier survival curves will be prepared.

Frequency of pulmonary exacerbations will be compared with frequency in the year prior to the trial.

Primary Endpoint:

- NTM sputum culture conversion to negative (defined as at least three consecutive negative mycobacterial cultures collected at least 4 weeks apart during the Treatment period).

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

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 to negative (defined as at least three consecutive negative AFB stained sputum smears on microscopy, collected at least 4 weeks apart in subjects who were smear positive at Baseline) during the Treatment period.
- Consistent sputum smear conversion to negative (defined as multiple consecutive negative but no positive smears after smear conversion and until the End of Treatment (Week 48) in subjects who were smear positive at Baseline).
- Durable NTM sputum smear conversion to negative without subsequent positive smears at Week 12 after End of Treatment.

Endpoints that are of the form “cure” (and similar) will be presented in the same way as the primary endpoint. This includes:

- NTM sputum culture microbiological cure (defined as multiple consecutive negative but no positive cultures with the causative species after culture conversion and until the End of Treatment (Week 48)).

- Durable NTM sputum microbiological cure for the NTM isolate(s) treated without recurrence at Week 12 after End of Treatment.

Semi-quantitative grading:

- The change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to End of Treatment and Week 12 after End of Treatment will be cross-tabulated in 5-by-5 tables of negative, scant, 1+, 2+, or 3+ comparing Baseline to each visit and to the follow-up visit. The number of subjects who decrease over the scale (and proportion out of the number per group) will be presented with 95% exact binomial confidence intervals.

The "time to event" endpoints will be summarized by Kaplan-Meier survival plots. The event will be regarded as having occurred at the time of the first consecutive negative culture:

- Time to first NTM sputum culture conversion during the Treatment period.
- Time to first NTM sputum smear conversion during the Treatment period.

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:

- Absolute change in FEV1 (percent predicted) from Baseline to End of Treatment and Week 12 after End of Treatment.
- Change in respiratory domain score assessed by CFQ-R from Baseline to End of Treatment and Week 12 after End of Treatment.
- Change in BMI from Baseline to End of Treatment and Week 12 after End of Treatment.

12.2. Safety Endpoints

All AEs will be summarized in total and for Groups 1, 2 and 3 separately.

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

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

12.3. 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, sorted by Group and subject and visit (when relevant).

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. 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 IRB, if required.

13.2. 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.

13.3. 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.

13.4. Audits and Inspections

Authorized representatives of Savara, a regulatory authority or an IRB 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, ICH GCP, and any applicable regulatory requirements. The Investigator should contact Savara immediately if contacted by a regulatory agency about an inspection.

13.5. Institutional Review Board (IRB)

The Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject 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 IRB.

14. ETHICS

14.1. Ethics Review

This protocol and any amendments will be submitted to a properly constituted IRB, in accordance with the ICH guidelines, and applicable national regulations, for approval/favorable opinion. An approval/favorable opinion must be obtained in writing before the first subject can be recruited.

14.2. 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.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data Management

Data management and handling of data will be conducted according to the trial specific Data Management Plan with ICH guidelines and 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 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.

15.2. 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 with the relevant dates (start and stop) and the action taken. Deviation reports will be kept in the Investigator's file and in the trial master file.

15.3. 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.

15.4. 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.

16. FINANCE AND INSURANCE

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IEC/IRBs or regulatory authorities in countries requiring this document.

17. TRIAL ORGANIZATION

The telephone numbers and fax numbers of relevant Sponsor staff, laboratories and other vendors are listed in the Investigator site file.

18. 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.

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20. APPENDICES

APPENDIX 1. RATIONALE FOR AMENDMENTS AND LIST OF REVISIONS

The protocol has undergone two amendments.

Table 5: Table of Revisions

Date	Version	Description of Document
23AUG2018	1.0	Final Protocol
01FEB2019	2.0	Updates based on Safety review of SAV008-01 and MOL-001 studies. A number of clarifications and administrative changes were also implemented.
12DEC2019	3.0	Removed the requirement for balanced enrollment in the MAC and MABSC subgroups 1, 2, and 3 Updated Sample Size A number of clarifications and administrative changes were also implemented.

APPENDIX 2. QUESTIONNAIRES

2.1 CYSTIC FIBROSIS QUESTIONNAIRE -REVISED

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**
CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

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

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

Section I. Demographics

Please fill-in the information or check the box indicating your answer.

A. What is your date of birth?
Date ☐☐ ☐☐ ☐☐☐☐
Mo Day Year

B. What is your gender?
☐ Male ☐ Female

C. During the **past two weeks**, have you been on vacation or out of school or work for reasons **NOT** related to your health?

☐ Yes ☐ No

D. What is your current marital status?
- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

E. Which of the following best describes your racial background?
- ☐ Caucasian
- ☐ African American
- ☐ Hispanic
- ☐ Asian/Oriental or Pacific Islander
- ☐ Native American or Native Alaskan
- ☐ Other (please describe) _____
- ☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?
- ☐ Some high school or less
- ☐ High school diploma/GED
- ☐ Vocational school
- ☐ Some college
- ☐ College degree
- ☐ Professional or graduate degree

G. Which of the following best describes your current work or school status?
- ☐ Attending school outside the home
- ☐ Taking educational courses at home
- ☐ Seeking work
- ☐ Working full or part time (either outside the home or at a home-based business)
- ☐ Full time homemaker
- ☐ Not attending school or working due to my health
- ☐ Not working for other reasons

CFQ-R **Adolescents and Adults** (Patients 14 Years Old and Older)
CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section II. Quality of Life

Please check the box indicating your answer.

*During the past **two weeks**, to what extent have you had difficulty:*	A lot of difficulty	Some difficulty	A little difficulty	No difficulty
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, groceries, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

***During the past two weeks**, indicate how often:*	Always	Often	Sometimes	Never
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt energetic	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

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

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking?
1. You can walk a long time without getting tired
2. You can walk a long time but you get tired
3. You cannot walk a long time because you get tired quickly
4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

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

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**
CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

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

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

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*	Very true	Somewhat true	Somewhat false	Very false
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, advancing in a job, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section III. School, Work, or Daily Activities

Questions 35 through 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?

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

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **two weeks**.*	**A great deal**	**Somewhat**	**A little**	**Not at all**
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus?	☐	☐	☐	☐ **Go to Question 44**

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*How often during the past **two weeks**:*	**Always**	**Often**	**Sometimes**	**Never**
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with gas?	☐	☐	☐	☐
48. Have you had diarrhea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Cystic Fibrosis Foundation