MOLGRAMOSTIM NEBULIZER SOLUTION

STATISTICAL ANALYSIS PLAN

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)

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1 SIGNATURE PAGE

The signatures below indicate that these individuals have reviewed this project specific Statistical Analysis Plan and consent to this document as governing the tasks outlined within. The signatures below also indicate that the processes and quality standards set forth by this Statistical Analysis Plan are approved for use in this study.

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4 ABBREVIATIONS AND DEFINITIONS

Abbreviation or Specialist Term	Explanation
AFB	Acid Fast Bacilli
ADR	Adverse Drug Reaction
AE	Adverse Event
ATS	American Thoracic Society
BMI	Body Mass Index
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
CT	Computed Tomography
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GLI	Global Lung Function Initiative
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IDSA	Infectious Diseases Society of America
IMP	Investigational Medicinal Product
LLOQ	Lower Limit of Quantification
MABSC	M. abscessus Complex
MAC	M. avium Complex

MedDRA	Medical Dictionary for Regulatory Activities
NTM	Nontuberculous Mycobacteria
NTM-PD	Nontuberculous Mycobacterial Pulmonary Disease
NYHA	New York Heart Association
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PT	Preferred Term
Q1	1st Quartile (25th Percentile)
Q3	3rd Quartile (75th Percentile)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
WBC	White Blood Cells

5 INTRODUCTION

5.1 Preface

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 disease recurred 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 recurrence after apparent cure is desperately required [Griffith 2016].

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 three groups of subjects, all with a confirmed CF diagnosis and chronic pulmonary NTM infection: 1. subjects who are on NTM antimycobacterial therapy who have not consistently achieved negative NTM sputum cultures; 2. subjects who are not on NTM antimycobacterial therapy as they 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; and 3. subjects who are not on NTM antimycobacterial therapy as they do not meet established guidelines for treatment despite persistent sputum culture positivity (ref: ATS position statement, CF guidelines). An increased risk of death has been shown with both NTM-pulmonary disease (hazard ratio 1.63) and NTM isolation without pulmonary disease (hazard ration 1.33) compared to matched controls

[Marras 2013]. Thus, there is a rationale for treatment also of the previously untreated group of patients.

5.2 Purpose of the analyses

As described in the protocol the analyses will assess the efficacy and safety of inhaled molgramostim in the three groups of subjects. Results will be included in the clinical study report.

6 SUMMARY OF CHANGES TO THE PLANNED ANALYSES

The protocol states that the statistical analyses will be conducted on the three groups of subjects separately. In addition, (not described in the protocol) the analyses will also assess the efficacy and safety of inhaled molgramostim in the overall group of subjects combining the three described groups.

According to the protocol, secondary efficacy analyses in the form of "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 at each assessment visit. The SAP expands these analyses by also including statistics for the mean, standard deviation (SD), 25th percentile (Q1), and 75th percentile (Q3).

Additional analyses not covered in the protocol are included in the SAP for elucidation of all safety data collected. These analyses include Summary of and Change from Baseline in FVC, FEV1/FVC, Vital Sign parameters, and ECG parameters.

Although the protocol states that a minimum of 30 subjects are to be enrolled, the study terminated early (with 14 subjects) due to COVID-19, with concerns related to challenges in recruitment, continued participation, and site operations. Due to this early termination, not all patients have completed the planned 48-week treatment period and some specified analyses may have insufficient data (e.g., CT scans, anti-drug antibodies, clinically significant decrease in FEV1 % predicted).

The protocol states that "A scoring system for central reading of the scans will be defined at a later timepoint." In view of the early termination of the trial, the low number of enrolled subjects, and CT being an exploratory endpoint only, a scoring system for central reading will not be defined after all. Instead, CT scans will be evaluated by whether they are reported as Normal, Abnormal but Not Clinically Significant, or Abnormal and Clinically Significant.

"Development of anti-drug antibodies during Treatment period and Follow-up period" is included as safety endpoint 7.5 in the protocol. However, as a validated assay is not available currently (nor in the foreseeable future) this endpoint will not be included after all.

The safety endpoint 7.3 "A clinically significant decrease in FEV1 (% 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)." is included in the protocol, but has been removed from the planned analyses due to lack of process for obtaining this information as well as low sample-size and premature trial termination.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study objectives

There are 13 objectives in the study, numbered [1] to [13]. Endpoints addressing these objectives are listed in section 7.2. Objectives [8] and [9] are subgroup analyses using subgroup variables in section 10.2 and relevant endpoints from section 7.2.

7.1.1 Primary objectives

To investigate efficacy of inhaled molgramostim on NTM sputum culture conversion to negative. [objective 1]

7.1.2 Secondary objectives

- To investigate efficacy of inhaled molgramostim on NTM sputum smear conversion to negative. [objective 2]
- To investigate efficacy of inhaled molgramostim on reduction of NTM bacterial load in sputum. [objective 3]
- To investigate efficacy of inhaled molgramostim on pulmonary function. [objective 4]
- To investigate efficacy of inhaled molgramostim on patient reported outcomes. [objective 5]
- To investigate efficacy of inhaled molgramostim on body mass index (BMI). [objective 6]
- To investigate safety of inhaled molgramostim in subjects with NTM infection. [objective 7]

7.1.3 Exploratory objectives

- To investigate efficacy in subjects infected with *M. abscessus* complex (MABSC) and *M. avium* complex (MAC), respectively. [objective 8]
- To investigate efficacy in subjects on concurrent anti-mycobacterial treatment and subjects not on anti-mycobacterial treatment, respectively. [objective 9]
- To investigate rates of recurrence and reinfection after End of Treatment. [objective 10]
- To investigate efficacy of inhaled molgramostim on bacterial co-infections. [objective 11]
- To investigate efficacy of inhaled molgramostim on frequency of pulmonary exacerbations. [objective 12]
- To investigate efficacy of inhaled molgramostim on morphologic findings on computed tomography (CT) scans of the lung. [objective 13]

7.2 Endpoints

The endpoints are numbered [*a*.*b*] where *a* labels the objective (numbering in section 7.1) and *b* is a numbering for the endpoint addressing the objective *a*.

7.2.1 Efficacy endpoints

7.2.1.1 Primary efficacy endpoint:

- Proportion 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). [endpoint 1.1]

7.2.1.2 Secondary efficacy endpoints:

- Proportion of subjects with 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)). [endpoint 1.2]
- Time (weeks) to first NTM sputum culture conversion during the Treatment period. [endpoint 1.3]
- Proportion of subjects with 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. [endpoint 2.1]

- Proportion of subjects with 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). [endpoint 2.2]
- Time (weeks) to first NTM sputum smear conversion during the Treatment period. [endpoint 2.3]
- Proportion of subjects with durable NTM sputum microbiological cure for the NTM isolate(s) treated without recurrence at Week 12 after End of Treatment. [endpoint 1.4]
- Proportion of subjects with durable NTM sputum smear conversion to negative without subsequent positive smears at Week 12 after End of Treatment. [endpoint 2.4]
- 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. [endpoint 3.1]
- Absolute change in FEV_1 (percent predicted) from Baseline to End of Treatment and Week 12 after End of Treatment. [endpoint 4.1]
- 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. [endpoint 5.1]
- Change in BMI from Baseline to End of Treatment and Week 12 after End of Treatment. [endpoint 6.1]

7.2.1.3 Exploratory Endpoints:

- Change from Baseline in time to positivity on NTM liquid culture media at Treatment visits and Follow-up. [endpoint 1.5]
- Change in semi-quantitative grade of sputum cultures from Baseline to Treatment visits and Follow-up. [endpoint 3.2]
- Proportion 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). [endpoint 10.1]
- Proportion of subjects with eradication and/or reduction in bacterial load of co-infections in sputum. [endpoint 11.1]
- Frequency of pulmonary exacerbations compared to the previous year. [endpoint 12.1]
- Change in CFQ-R scores for each of the HrQoL domains (physical functioning, vitality, health perceptions, treatment burden, body image, eating, role functioning, emotional functioning, social functioning), each of the Symptoms domains, except respiratory, (weight and digestion)[endpoint 5.2]

- Change in CT scans of the lungs from Baseline to End of Treatment (Week 48). [endpoint 13.1]

7.2.2 Safety endpoints

- Number of AEs, serious adverse events (SAEs), adverse drug reactions (ADRs), severe AEs and AEs leading to treatment discontinuation during the trial period. [endpoint 7.1]
- Change in white blood cell counts (WBC) and differentials in blood from Baseline to Treatment visits. [endpoint 7.2]
- GM-CSF concentration levels during Treatment period. [endpoint 7.4]

7.3 Derived variables

7.3.1 NTM sputum culture conversion to negative

Inclusion criterion 6 requires the sputum culture to be positive for the same species (MAC) or subspecies (MABSC) of NTM at Screening and Baseline. Therefore, the causative species/subspecies is identified at Screening and confirmed at Baseline.

A sputum culture conversion to negative is defined as having a negative result[(a)] on 3 or more consecutive on-treatment visits[(b)] that are at least 4 weeks apart.

(a) A negative result is defined as being negative for the causative species/subspecies, even if it is positive for a non-causative species/subspecies.
(b) Subjects may experience more than 1 conversion. The start of a conversion is the date of the first negative visit. The first negative visit must occur during the treatment period, i.e. between first dose of study drug (inclusive) to last dose of study drug (inclusive). After a run of at least 3 consecutive negative visits, the end of a conversion is followed by a next visit with positive result. The end of the conversion is the date of the last negative visit.
(c) The criterion that each of the 3 consecutive monthly visits should be at least 4 weeks (i.e. within the allowed visit windows) apart will be upheld. Since visit windows are 28±7 days, the 3 consecutive visit duration can range from 43 to 71 days.

The primary endpoint Sputum Culture Conversion to Negative [endpoint 1.1] is defined as having at least 1 sputum culture conversion to negative.

7.3.2 NTM sputum smear conversion to negative

Inclusion/exclusion criteria do not require the sputum smear to have a positive acid-fast bacilli (AFB) stain at Screening and Baseline. Therefore, subjects can be smear negative at Baseline.

A sputum smear conversion to negative is defined as having a negative result[(a)] on 3 or more consecutive on-treatment visits[(b)] that are at least 4 weeks apart[(c)]. in a subject who was smear positive at Baseline.

(a) A negative result is defined as a negative AFB stained sputum smear on microscopy.
(b) Subjects may experience more than 1 conversion. The start of a conversion is the date of the first negative visit. The first negative visit must occur during the treatment period, i.e. between first dose of study drug (inclusive) to last dose of study drug (inclusive). (Note, the baseline smear result is not considered even if the subject had a smear negative result at Baseline.) After a run of at least 3 consecutive negative visits, the end of a conversion is followed by a next visit with positive result. The end of the conversion is the date of the last negative visit.
(c) The criterion that each of the 3 consecutive visits should be at least 4 weeks (within the allowed visit windows) apart will be upheld. Since visit windows are 28±7 days, the 3 consecutive visit duration can range from 43 to 71 days.

The secondary endpoint of Sputum Smear Conversion to Negative [endpoint 2.1] is defined as having at least 1 sputum smear conversion to negative.

7.3.3 Time to conversion

Time to sputum culture conversion [endpoint 1.3] will be calculated as:

(Date of first negative visit of the first culture conversion)-(Date of first dose)+1

Time to sputum smear conversion [endpoint 2.3] will be calculated as:

(Date of first negative visit of the first smear conversion)-(Date of first dose)+1

7.3.4 NTM sputum culture microbiological cure and Consistent NTM sputum smear conversion to negative (on-treatment)

Sputum culture microbiological cure [endpoint 1.2] is defined as having all visits from the last culture conversion and until End of Treatment (EOT) be negative for the causative species/subspecies. Note, EOT (See section 8.3.2 for definition of EOT). Only subjects with culture conversion to negative can potentially experience microbiological cure.

Assessment of culture microbiological cure will consider only the on-treatment scheduled and on-treatment unscheduled visits.

Consistent sputum smear conversion to negative [endpoint 2.2] is defined similar to sputum culture microbiological cure but based on sputum smear results.

7.3.5 Durable NTM sputum microbiological cure for NTM isolates & Durable NTM sputum smear conversion to negative (off-treatment)

Durable sputum microbiological cure for NTM isolates [endpoint 1.4] is defined as having negative culture at EOT and negative results at all visits up to the Follow up Week 12 visit. Only subjects with culture conversion to negative during the treatment period (and microbiological cure during the remainder of the treatment period if applicable) can potentially experience durable microbiological cure.

Durable sputum smear conversion to negative [endpoint 2.4] is defined similar to durable sputum microbiological cure for NTM isolates but based on sputum smear results.

7.3.6 Change in semi-quantitative grade

Semi-quantitative grades are (negative, scant, 1+, 2+, 3+) assessed at Screening, Baseline, Treatment Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48/EOT, and Follow-up Weeks 4, 12, and 24. Sputum smear data are collected using the semi-quantitative grades directly, as presented as follows:

- No AFB found
- 1+ = 2 to 18 AFB/50 fields observed
- 2+ = 4 to 36 AFB/10 fields observed
- 3+ = 4 to 36 AFB/fields observed
- 4+ >36 AFB/fields observed

Sputum culture data are categorized into the semi-quantitative grades as follows:

- Negative = 0 colonies
- Scant = 1-5 colonies
- 1+ = 5-25 colonies
- 2+ = 25-100 colonies
- 3+ = 100-200 colonies
- 4+ >200 colonies

Shifts between (negative, scant, 1+, 2+, 3+) categories will be used to describe change from baseline to each treatment visit and each follow-up visit in semi-quantitative grade for sputum smear [endpoint 3.1] and sputum culture [endpoint 3.2].

Categorized decrease will be defined as shift from grade (scant, 1+, 2+ or 3+) to any lower grade.

7.3.7 Time to positivity

The time to positivity on NTM liquid culture media will be assessed for each sputum culture. Since this is time to event type data, the distribution of the data may not be normally distributed. In addition, to calculating the absolute change from baseline [endpoint 1.5], the fold change = (post-baseline)/(baseline) will be calculated for analysis.

7.3.8 FEV1% predicted

Pulmonary function tests (FEV1, FVC and FEV1/FVC) are assessed at Screening, Baseline (pre-dose, 1.5h post-dose), Treatment Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48/EOT, and Follow-up Weeks 4, 12, 24.

The absolute change from baseline in FEV1% predicted [endpoint 4.1] will be calculated.

7.3.9 Cystic Fibrosis Questionnaire-Revised (CFQ-R)

CFQ-R (Teen/Adult version) containing 50 items is assessed at Baseline, Treatment Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48/EOT, and Follow-up Weeks 4, 12, 24. The items will be used to derive 9 quality of life domains (physical, role, vitality, emotion, social, body image, eating, treatment burden, health perceptions) and 3 symptom scales (weight, respiratory, and digestion). The scoring instruction instructions for the domains/symptom scales are in Appendix section 19.1.

Absolute change from baseline in the respiratory symptom scale [endpoint 5.1] will be analyzed as a secondary endpoint.

Absolute change from baseline in the remaining domains (physical, role, vitality, emotion, social, body image, eating, treatment burden, health perceptions, weight, and digestion) will be analyzed as exploratory endpoints [endpoints 5.2].

7.3.10 Body mass index

Height is assessed at Screening only. Weight is assessed at Baseline, Treatment Weeks 1, 2, 4, 8, 12, 16, 20, 24, 24, 28, 32, 36, 40, 44 and, 48/EOT, and Follow-up Weeks 4, 12, 24. BMI is calculated as (weight kg)/(height m)^2. The absolute change from baseline in BMI [endpoint 6.1] will be calculated.

7.3.11 Recurrence or reinfection after EOT

Recurrence will be defined as having two sputum cultures positive for the causative species/subspecies after EOT in subjects who have achieved microbiological cure at EOT.

Reinfection will be defined as having two sputum cultures positive for any non-causative species/subspecies after EOT in subjects who have achieved microbiological cure at EOT.

The exploratory endpoint is defined as having either recurrence or reinfection [endpoint 10.1].

Assessment of recurrence and reinfection will consider only the follow-up visits.

7.3.12 Eradication and/or reduction in bacterial load of co-infections

Co-infection is identified as having a positive culture with non-causative bacteria (i.e. not NTM).

Bacterial load is quantified as:

1+ = rare growth

2+ = light growth

3+ = moderate growth

4+ = heavy growth

UNK = Unknown

Reduction is defined as a decrease of at least 1 grade in the bacterial load. Eradication is defined as having no growth or organism not present.

Therefore, the exploratory endpoint is defined as having a reduction of at least 1 grade in bacterial load of the non-causative organism(s). [endpoint 11.1] This will be calculated at each visit.

7.3.13 Annual rate of pulmonary exacerbation

Number of pulmonary exacerbation events within the last year prior to baseline will be estimated in respiratory history CRF.

The incidence rate (events per year) of pulmonary exacerbation events during the study will be calculated as the number of pulmonary exacerbation treatment-emergent adverse events divided by the length (years) of adverse event observation period ([date of study completion/early withdrawal – date of first dose + 1]/365.25). Pulmonary exacerbation events occurring during the treatment-emergent period will be identified using MedDRA search criteria (Appendix section 19.2).

The ratio of the annual rate during the study to the annual rate last year will be constructed for each subject. [endpoint 11.1]

7.3.14 Change in CT scan interpretation

CT scan is assessed at Baseline and Week 48/EOT. Change from baseline will be described by shift in categories of CT scan interpretation: normal, abnormal not clinically significant (NCS), abnormal clinically significant (CS).

7.3.15 Change in WBC and differentials

WBC and differentials are assessed at Screening, Baseline*, Treatment Weeks 1*, 2*, 4*, 8, 12*, 16, 20, 24*, 28, 32, 36*, 40, 44, 48*/EOT*, and Follow-up Weeks 4, 12, 24. At visits annotated with *, the WBC and differentials are assessed at pre-dose and 2h post-dose.

Absolute change from baseline will be calculated using the Day 1 pre-dose as baseline. [endpoint 7.2]

In addition, the absolute change from same day pre-dose baseline will be calculated on visits annotated with *.

7.3.16 GM-CSF concentration

GM-CSF is assessed at Baseline*, Treatment Weeks 2*, 12*, 24*, 36*, 48*/EOT* and Follow-up Weeks 12, 24. Visits annotated with * have GM-CSF is assessed at pre-dose and 2h post-dose.

The following GM-CSF concentration levels are assessed: pre-dose baseline, Cmin (pre-dose during treatment), Cmax after dosing (2h post-dose during treatment) and at 12 and 24 weeks after last dose. [endpoint 7.4]

8 STUDY METHODS

8.1 General study design and plan

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

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 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 Disease 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).

Subjects in all 3 groups will receive open-label treatment with inhaled molgramostim given at a dosage of 300 μg once daily for 48 weeks administered via the Investigational eFlow Nebulizer System.

All subjects will have a 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, 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.

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
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	
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				

	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	
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)
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 12.12.1.

[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 accepted. If Early End of Treatment Visit occurs prior to or at Week 12, then a CT scan is not required at Early End of Treatment Visit. 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] WBC 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.

8.2 Inclusion-exclusion criteria and general study population

8.2.1 Subject 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 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.

8.2.2 Subject 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 medication, 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.

8.3 Study variables

8.3.1 Study day

Study day of assessments or events is calculated as:

- Date of assessment – date of first dose + 1, if date of assessment ≥ date of first dose.
- Date of assessment – date of first dose, if date of assessment < date of first dose.

8.3.2 End of treatment (EOT) visit

For subjects treated up to Week 48, end of treatment (EOT) visit is the assessment at the Treatment Week 48 visit.

For subjects who discontinued study drug prior to Week 48, EOT is the assessment at the last on-treatment scheduled or unscheduled visit.

In summary tables,

- Week 48 will display data occurring at the planned Week 48 time point for subjects who complete a full 48-week treatment period.
- EOT visit will be display data for subjects with early end of treatment as well as subjects who complete a full 48-week treatment period.

8.3.3 Treatment period and Follow-up period

The treatment period starts from date of first dose of study drug and ends on date of last dose. The follow-up period starts from date of last dose + 1 day and ends at the last follow-up visit.

8.3.4 Visit windows

Please reference Table 1 for scheduled visit windows and corresponding study days.

If an assessment occurs outside of these scheduled visit windows and a visit name/number has not been provided in the raw data, then the assessment should be mapped to the nearest visit (which does not already have a corresponding assessment) that occurred either immediately before or after the assessment's study day.

If multiple assessments occur within the same assessment time window, then the assessment nearest to the scheduled visit date will be retained for analysis. If there is a tie, the later visit will be retained.

8.3.5 Baseline value

Baseline will be defined as the last non-missing value prior to administration of first dose of study drug.

9 SAMPLE SIZE

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. The sample size consideration by group is summarized in Table 2.

Table 2: Number of Subjects

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

10 GENERAL CONSIDERATIONS

10.1 Analysis Populations

The All Subjects analysis set will include all subjects with informed consent.

The Safety Analysis Set (SAF) will include all subjects who received at least 1 dose of study drug.

The Pharmacokinetic Analysis Set (PKAS) will include all subjects who received at least 1 dose of study drug for whom at least 1 quantifiable plasma concentration of GM-CSF with known sample date and time is obtained.

10.2 Covariates and Subgroups

There subgroup variables are numbered [*a*.*b*] where *a* labels the objective (numbering in section 7.1) and *b* is a numbering for the subgroup variable addressing the objective *a*.

The following subgroup variables will be defined:

- Causative species (MABSC, MAC). [subgroup 8.1]
- Any concurrent anti-mycobacterial medication during the treatment period (Yes, No). [subgroup 9.1]

A concurrent anti-mycobacterial medication during the treatment period is a medication with standard medication name (CMDECOD) listed in Appendix section 19.3 and having at least one dose taken between the date of first dose (inclusive) and the last dose of study drug (inclusive).

10.3 Missing Data

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the start and stop dates of AEs and medication (described below). The imputed dates will be used to determine whether an AE is treatment emergent, and

whether a medication is prior and/or concomitant. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

10.3.1 Imputation of Adverse Start Event Dates

Missing or partial AE start dates will be imputed with consideration of start of the treatment period:

1. *If AE start date is missing day element:*

- If available AE start MONYEAR = study treatment start month/year then:
    - If AE stop date contains a complete date and stop date is before study treatment start date then set AE start date = 01MONYEAR.
    - If AE stop date is (complete stop date is on or after study treatment start date) or (partial stop month/year is on or after study treatment start month/year) or (partial stop year is on or after study treatment start year) or (missing entire stop date) then set AE start date = study treatment start date.
- If available AE start MONYEAR ≠ study treatment start month/year then set AE start date = 01MONYEAR.

2. *If AE start date is missing day and month elements:*

- If available AE start YEAR = study treatment start year then:
    - If AE stop date (complete stop date is before study treatment start date) or (partial stop month/year is before study treatment start month/year) then set AE start date = 01JANYYYY.
    - If AE stop date is (complete stop date is on or after study treatment start date) or (partial stop date MONYYYY is on or after study treatment start MONYYYY) or (partial stop date YYYY is on or after study treatment start YYYY) or (missing entire stop date) then set AE start date = study treatment start date.
- If available AE start YEAR ≠ study treatment start year then set AE start date = 01JANYEAR.

3. *If AE start date is missing day, month and year elements:*

- If AE stop date (complete stop date is before study treatment start date) or (partial stop month/YEAR is before study treatment start month/year) or (partial stop YEAR is before study treatment start year) then set AE start date = 01JAN of the stop YEAR.
- If AE stop date is (complete stop date is on or after study treatment start date) or (partial stop date month/year is on or after study treatment start month/year) or (partial stop date year is on or after study treatment start year) or (missing entire stop date) then set AE start date = study treatment start date.

The imputation algorithm for AE start dates is summarized in Table 3.

Table 3 Imputation of AE start dates

Start Date		Stop Date						
		Complete: DDMONYEAR		Partial: MONYEAR		Partial: YEAR		
		< 1st dose	≥ 1st dose	< 1st dose MONYEAR	≥ 1st dose MONYEAR	< 1st dose YEAR	≥ 1st dose YEAR	Missing
Partial: MONYEAR	= 1st dose MONYEAR	B	A	na	A	na	A	A
	≠1st dose MONYEAR		B	B	B	B	B	B
Partial: YEAR	= 1st dose YEAR	C	A	C	A	na	A	A
	≠1st dose YEAR		C		C	C	C	C
Missing		D	A	D	A	D	A	A

A = Impute AE start date as the date of first dose; B = Impute AE start date as the first of the month;
C = Impute AE start date as 01 January of the year; D = Impute AE start date as 01 January of the stop year;
na = Missing data case is not applicable.

10.3.2 Imputation of Adverse Event Stop Dates

Missing or partial AE stop dates will be imputed with consideration of end of the treatment period:

1. *If AE stop date is missing day element:* Impute as min(Last day of that month, Date of end of treatment period).
2. *If AE stop date is missing day and month elements:* Impute as min(31 December of that year, Date of end of treatment period).
3. *If AE stop date is entirely missing*: Impute as Date of end of treatment period.

10.3.3 Imputation of Start and End Dates for Prior/Concomitant Medication and Surgical Procedures

Missing or partial medication start and stop dates of medications and surgical procedures will be imputed with consideration of the start of the baseline period and end of the treatment period:

If start date is missing or partial:

- If day is missing, use the first day of the month under consideration.
- If month is missing, use January.
- If year is missing, use year of the informed consent date.
- If entire date is missing, use informed consent date.

If stop date is missing or partial and medication is not ongoing:

- if day is missing, use the last day of the month under consideration.

- if month is missing, use December.
- if year or the entire date is missing, set to 31 December 2099

If the imputed start date is after the stop date, then the imputed start date will be revised to be one day prior to the stop date. If the medication is indicated as ongoing, the stop date will remain

10.4 Interim Analyses and Data Monitoring

No interim analyses are planned.

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. The statistical methodology and outputs for these data review meetings are defined in the SDRC charter.

10.5 Multiple Testing

There will be no hypothesis tests performed and no comparisons statistics estimated between the patient groups. All analyses are descriptive within each patient group. Consequently, no adjustments for multiplicity will be required.

11 SUMMARY OF STUDY DATA

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD), median, 25^{th} percentile (Q1), 75^{th} percentile (Q3), minimum and maximum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

Data listings will show all recorded data, sorted by group (Group 1, Group 2, Group 3 who were treated and then Group 1, Group 2, Group 3 screen failures) and subject and visit (when relevant).

All summary tables will be structured with a column for each group (Group 1, Group 2, Group 3) and overall (All Subjects) and will include in the header the total population size relevant to that table/treatment, including any missing observations.

11.1 Subject Disposition

The subject disposition will be summarized by group and overall based on All Subjects for the number of subjects who were screened, failed screening, were treated, discontinued

treatment, completed the study, discontinued from the study, and reasons for discontinuation.

A by-subject data listing of study completion information including the reason for study discontinuation will be presented for All Subjects.

11.2 Protocol Deviations

Protocol deviations will be presented in a by-subject data listing for All Subjects who have at least 1 protocol deviation. Since analysis groups are defined based on NTM infection characteristics, protocol deviations will not have an impact on which subjects are included in each group, as defined in section 10.1.

11.3 Demographic and Baseline Variables

Demographic characteristics including age at informed consent, sex, ethnicity, race, and smoking status will be summarized by group and overall for SAF.

Baseline characteristics including causative species (MABSC, MAC) [subgroup 8.1] and causative subspecies (MABSC subspecies: M. abscessus subsp. abscessus, M. abscessus subsp. massiliense, M. abscessus subsp. bolletii, Unknown; MAC subspecies: M. intracellulare, M. avium, Other MAC, Unknown) will also be summarized.

A by-subject data listing of demographic and baseline characteristics will also be presented for All Subjects.

11.4 Concurrent Illnesses and Medical Conditions

Medical History events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary 22.1 or later. These events will be presented in a by-subject data listing for All Subjects.

11.5 Prior and Concurrent Medications

Prior and concomitant medications will be coded using WHO drug dictionary version Mar 2019 or later.

Medications can only be flagged as prior or concurrent:

Prior medication is defined as any medication with a stop date prior to the date of first dose of study drug. Concurrent medication during the treatment period is defined as medication with stop date between the date of first dose (inclusive) of study medication and the last dose of treatment (inclusive).Prior and concomitant medications will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by group and overall for SAF. Patients taking the same medication multiple times will be counted once per medication and investigational period. In case a medication

is classified into several chemical and/or therapeutic subgroups, it will be presented in all chemical and therapeutic subgroups.

In addition, any concurrent anti-mycobacterial medication during the treatment period (Yes, No) [subgroup 9.1] will be summarized by group and overall for SAF.

A by-subject data listing will be presented for all prior and concurrent medications for All Subjects.

11.6 Treatment Compliance

Treatment compliance will be calculated at Treatment Weeks x=4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and,48 (EOT is not applicable), as well as overall.

$$\text{Compliance at Week } x = \left(\frac{\left(\text{Number of used vials returned at Week } x\right) + \left(\text{Number of non-returned vials at Week } x\right)}{\left(\text{Number of days between treatment visits}\right)}\right) \times 100\%$$

$$\text{Overall Compliance} = \left(\frac{\left(\text{Number of used vials returned in total}\right) + \left(\text{Number of non-returned vials in total}\right)}{\left(\text{Number of days between first IP administration and last IP return}\right)}\right) \times 100\%$$

Treatment compliance will be summarized for SAF by presenting the number of vials dispensed and vials used (sum of returned and lost) at each regularly scheduled visit and presenting the % compliance at each regularly scheduled post-baseline visit. The number of vials dispensed, vials used (returned and lost), and % compliance will also be totaled across all visits.

Number of vials dispensed, used vials returned, unused vials returned, used vials lost, unused vials lost, and the weekly and overall compliance will be listed for SAF.

12 EFFICACY ANALYSES

Each group (Group 1, Group 2 and Group 3) and the overall group 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.

12.1 Primary Efficacy Analysis

The proportion of subjects with sputum culture conversion to negative [endpoint 1.1] (number of subjects who convert to negative out of the number per group) will be presented with 95% exact binomial confidence intervals. This proportion will be calculated by group and overall for SAF.

12.2 Secondary Efficacy Analyses

12.2.1 Overall Response Variables

The number (%) of subjects and 95% exact binomial confidence interval for the proportion will be calculated by group and overall for SAF for the following endpoints:

- Sputum smear conversion to negative [2.1]*.
- NTM sputum culture microbiological cure [endpoint 1.2]
- Consistent sputum smear conversion to negative [endpoint 2.2]*.
- Durable NTM sputum microbiological cure for the NTM isolates [endpoint 1.4].
- Durable NTM sputum smear conversion to negative [endpoint 2.4]*.

*Sputum smear conversion to negative is only possible provided subjects were sputum smear positive at baseline.

12.2.2 By-Visit Response Variables

For semi-quantitative grading of the number of NTM on microscopy of AFB stained sputum smears [endpoint 3.1], a shift table displaying the number (%) of subjects with shifts from Baseline in 5 categories (negative, scant, 1+, 2+, or 3+) will be summarized for treatment visits (Weeks, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48*, EOT*) and follow-up visits (Follow-up Weeks 4, 12*, 24) by group and overall for SAF.

*These time points being of specific interest.

The number (%) of subjects with categorized decrease in semi-quantitative grading of sputum smear will be summarized at each visit by group and overall for SAF. A 95% exact binomial confidence interval will be presented for the proportion of subjects with categorized decrease.

12.2.3 Time to Event Variables

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. [endpoint 1.3]
- Time to first NTM sputum smear conversion during the Treatment period. [endpoint 2.3]

12.2.4 Continuous Variables

The following continuous endpoints will be presented using mean, SD, median, Q1, Q3, min and max at baseline and each assessment visit; and mean, SD, median, min and max change from Baseline to each assessment visit by group for SAF:

- Absolute change in FEV1% predicted from Baseline (pre-dose) to 1.5h post-dose, Treatment Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and, 48*, EOT*, and Follow-up Weeks 4, 12*, 24. [endpoint 4.1]
- Absolute change in CFQ-R respiratory symptom scale from Baseline to Treatment Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and, 48*, EOT*, and Follow-up Weeks 4, 12*, 24. [endpoint 5.1]
- Absolute change in BMI from Baseline to Treatment Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48*, EOT*, and Follow-up Weeks 4, 12*, 24. [endpoint 6.1]

*These time points being of specific interest.

12.3 Exploratory Efficacy Analyses

12.3.1 Overall Response

The number (%) of subjects will be presented by group and overall for SAF for any recurrence or reinfection after EOT.

12.3.2 By-Visit Response

For semi-quantitative grading of sputum culture [endpoint 3.2], a shift table displaying the number (%) of subjects with shifts from Baseline in 5 categories (negative, scant, 1+, 2+, or 3+) will be summarized for treatment visits (Weeks, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and, 48, EOT) and follow-up visits (Follow-up Weeks 4, 12, 24) by group and overall for SAF.

The number (%) of subjects with categorized decrease in semi-quantitative grading of sputum culture will be summarized at each visit by group and overall for SAF. A 95% exact binomial confidence interval will be presented for the proportion of subjects with categorized decrease.

The number (%) of subjects with eradication and/or reduction in bacterial load of co-infections in sputum will be summarized at each visit by group and overall for SAF.

The number (%) of subjects with Normal, Abnormal NCS, Abnormal CS interpretation and shift from Baseline to Week 48 and EOT will be summarized by group and overall for SAF.

12.3.3 Continuous Variables

The following continuous endpoints will be presented as mean, SD, median, Q1, Q3, min and max at baseline and each assessment visit; and mean, SD, median, min and max change from Baseline to each assessment visit by group for SAF:

- Absolute change and fold change from Baseline in time to positivity on NTM liquid culture media at Treatment visits and Follow-up.
- Absolute change in CFQ-R domains scores for physical functioning, vitality, health perceptions, treatment burden, role functioning, emotional functioning, and social functioning.

The following continuous endpoint will be presented as mean, SD, median, Q1, Q3, min and max by group for SAF:

- Frequency of pulmonary exacerbations in the previous year, annual rate of pulmonary exacerbations during the study, rate ratio.

13 SAFETY ANALYSES

13.1 Extent of Exposure

13.1.1 Inhaled molgramostim

Duration (days) of exposure to inhaled molgramostim is calculated as (date of last dose of study drug)-(date of first dose of study)+1. Exposure duration will be categorized into 12 4-week intervals: 1 to 28 days, 29 to 56 days, ..., 281 to 308 days, ≥309 days (the last interval is open-ended to allow for maximum duration exceeding 336 days). Exposure duration (continuous and categorical) will be summarized by group and overall and listed for SAF.

13.1.2 Antimycobacterial therapy

Subjects in Group 1 will have concomitant antimycobacterial treatment. The antimycobacterial therapy should preferably not change during the treatment period except in case of drug toxicity or adverse reactions. All changes in antimycobacterial treatment will be recorded including planned daily dosing and actual daily drug intake, physician-prescribed modification and interruptions, and reasons for each change in antimycobacterial treatment.

Antimycobacterial therapy variables will be listed only.

13.2 Adverse Events, Serious Adverse Events, Deaths, and other Significant Adverse Events

AEs will be recorded from the time written informed consent is signed until 30 days after the last dose of study drug. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary 22.1 or later. It will be used to summarize AEs by system organ class (SOC) and preferred term (PT).

Treatment-emergent AE (TEAE) is defined as any AE that started or worsened in severity on or after the date of first dose of study drug until 30 days after the last dose or until the last follow-up visit, whichever is **longer**. AEs are considered treatment-emergent irrespective of

hour or minute of onset (if recorded). Imputed AE start dates are allowed for determination of treatment-emergence.

Related TEAE will be defined as any TEAE with “possible” or “probably” relationship to study treatment as assessed by the investigator or with “not applicable” or missing assessment of the causal relationship. AEs with start date before or after the

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

Key guidelines for counting incidence proportions of AEs are as follows:

- When a patient has the same AE reported multiple times during an analysis period based on MedDRA terminology (SOC or PT), the patient will only be counted once within a level of MedDRA in an AE incidence table.
- When assessing investigator reported relationship to study drug of the AEs, if an AE reported multiple times changes in causal relationship during an analysis period for a patient, the event with highest relatedness will be presented. Related AEs will include those reported as “possible” or “probably” by the investigator and those with a “not applicable” or missing relationship. However, in the summary of AEs by relationship, AEs with “not applicable” or missing relationship will be separate categories to be tabulated.
- When summarizing severity of the AEs (mild, moderate, severe), if there are multiple AEs of the same preferred term but different severity, during an analysis period for a patient, the AE with the maximum severity will be reported. If the AE term (SOC and PT) is reported more than once, one of them with missing severity, and at least another with non-missing severity, the maximum severity will be chosen from the non-missing severity and the missing severity can be ignored. If all are of missing severity, then the AE severity will be summarized with an additional “Missing” category. In summary of severe AEs, missing severity will be included in severe category following conservative approach.
- When summarizing severity for related AEs, only related AEs will be used in the analysis. If a patient has the same AE reported multiple times during an analysis period for a related AE, the AE with the maximum severity will be chosen.

In summaries by SOC and PT, AEs will be sorted alphabetically for SOC and descending frequency for PT in total patients. Summaries will include only TEAEs. All AEs, all SAEs and TEAEs leading to study drug discontinuation will be listed for SAF. Individual-subject narratives written for all SAEs.

13.2.1 Overview of TEAEs

An overview of AEs will summarize the number (%) of patients and number of events for the following details by group and overall for SAF:

- TEAEs
- Related TEAEs (i.e. adverse drug reactions (ADRs))
- Serious TEAEs

- Severe TEAEs
- TEAEs leading to study drug discontinuation
- Deaths

13.2.2 TEAEs by SOC and PT

The number (%) of patients with TEAEs classified by SOC and PT will be summarized by group and overall for SAF. Summaries will be provided for:

- TEAEs
- Related TEAEs
- Serious TEAEs
- Severe TEAEs
- TEAEs leading to study drug discontinuation

13.3 Pregnancies

Serum pregnancy test will be assessed at screening, day 1 (including urine pregnancy test), treatment week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 and EOT, and follow-up week 4.

A by-subject data listing will be provided for pregnancy data including if the pregnancy test was performed, result of the test (if performed), reason for test not performed, visit, and date/time of test.

13.4 Clinical Laboratory Evaluations

Details of laboratory assessments performed by the central laboratory are provided in Table 4. Hematology, biochemistry and urinalysis will be assessed at scheduled visits and optionally at unscheduled study visits.

Table 4: Safety laboratory tests

Test	Scheduled visit	Parameters to be analyzed
Hematology	V1/Screening; Pre-dose on V2/D1, V5/W4, V6/W8, ..., V15/W44, V16/W48; V17/FU4, V18/FU12, V19/FU19	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, and prothrombin time international normalized ratio (PT-INR).
	Pre-dose and 2 hours post-dose on V2/D1, V3/W1, V4/W2, V5/W4, V7/W12, V10/W24, V13/W36, V16/W48; Otherwise only pre-dose on the other scheduled visits	WBC count, and white cell differentials absolute count: neutrophils, lymphocytes, monocytes, eosinophils, basophils,
Biochemistry	V1/Screening; Pre-dose on V2/D1, V5/W4, V6/W8, ..., V15/W44, V16/W48; V17/FU4, V18/FU12, V19/FU19	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).
Urinalysis	V1/Screening; Pre-dose on V2/D1, V5/W4, V6/W8, ..., V15/W44, V16/W48; V17/FU4, V18/FU12, V19/FU19	pH, specific gravity, bilirubin, glucose, ketones, RBCs, WBCs, protein, microalbuminuria, and microscopic elements.

For laboratory safety continuous variables, values recorded as “<X” or “<=X” or “>Y” or “>=Y” will be imputed by “X” and “Y” respectively for descriptive statistics. This will be documented in a footnote in all output where such a replacement was performed.

Continuous clinical laboratory observed values and absolute change from baseline (for all hematology and biochemistry parameters and pH value and specific gravity from the urinalysis panel) at baseline and scheduled post-baseline visits (including EOT) and time points will be summarized by visit, treatment group and overall for SAF.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. The number (%) of subjects below and above reference range will be summarized by visit, treatment group and overall for SAF.

Categorical urinalysis variables will be summarized for the number (%) of subjects in each of the categories by visit, treatment group and overall for SAF.

All laboratory parameters will be presented in a by-subject data listing for SAF and will include the lab category, lab test, unit of measurement, test result, reference range indicator (e.g., normal, high, low), visit, date, time point (pre-dose, post-dose), and reason

test not performed (if applicable). All visits, including screening and unscheduled, will be included in the data listing.

13.4.1 Change from same visit baseline

For WBC count and white cell differentials, the change from same visit baseline to same visit 2-hour post-dose value will be calculated and summarized at treatment week 1, 2, 4, 12, 24, 36, 48.

13.5 Other Safety Measures

13.5.1 Pulmonary Function Test (PFT)

PFT including FEV1, FVC and FEV1% will be assessed at screening, pre-dose on day 1, and at 1.5 hours post-dose on day 1, treatment week 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and, 48, and follow-up week 4, 12, 24.

FEV1% predicted and absolute change from baseline will be summarized by visit (including EOT), treatment group and overall for SAF.

All PFT parameters will be presented in a by-subject data listing for SAF and will include FEV1, FVC, FEV1% and FEV1% predicted, visit, date, time point, and reason test not performed (if applicable). All visits, including screening and unscheduled, will be included in the data listing.

13.5.2 Vital signs

Vital signs including SBP (mmHg), DBP (mmHg), heart rate (beats per minute), respiration rate (breaths per minute), body temperature (°C) will be assessed at screening, pre-dose and 2 hours post-dose on day 1, treatment week 1, 2, 4, 12, 24, 36, 48, and pre-dose only on other scheduled visits.

Vital signs parameters, body weight and BMI (section 7.3.10) observed value and absolute change from baseline will be summarized by visit (including EOT), treatment group and overall for SAF.

In addition, for vital signs parameters, absolute change from same visit baseline will be summarized at treatment week 1, 2, 4, 12, 24, 36, 48.

All vital sign parameters will be presented in a by-subject data listing for SAF and will include the vital sign, unit of measurement, test result, visit, date, time point (pre-dose, post-dose), and reason test not performed (if applicable). Body weight and BMI will be similarly listed. All visits, including screening and unscheduled, will be included in the data listing.

13.5.3 Electrocardiogram (ECG)

12-lead ECGs continuous parameters include heart rate, QRS, PR, QT and QTcF intervals, and ECG interpretation (normal, abnormal NCS (not clinically significant), abnormal CS (clinically

significant)) will be assessed at screening, day 1, treatment week 4, 12, 24, 36, 48, and follow-up week 24.

ECG continuous parameter observed values and absolute change from baseline will be summarized by visit (including EOT), treatment group and overall for SAF.

ECG interpretation will be summarized for the number (%) of subjects in each of the categories by visit (including EOT), treatment group and overall for SAF. Shifts in categories (normal, abnormal NCS, abnormal CS) from baseline to post-baseline visits will be summarized by visit, treatment group and overall for SAF.

All ECG parameters will be presented in a by-subject data listing for SAF and will include the ECG parameter, unit of measurement, test result, visit, date, and reason test not performed (if applicable). All visits, including screening and unscheduled, will be included in the data listing.

13.5.4 Computed Tomography (CT)

CT scans of the lung will be assessed at day 1 and treatment week 48. CT interpretation will be summarized for the number (%) of subjects in each of the categories by visit, treatment group and overall for SAF. Shifts in categories (normal, abnormal NCS, abnormal CS) from baseline to week 48 will be summarized by visit (EOT*), treatment group and overall for SAF.

*If Early End of Treatment Visit occurs prior to or at Week 12, then a CT scan is not required at Early End of Treatment Visit.

All CT values will be presented in a by-subject data listing for SAF and will include the test result (normal/abnormal), clinical significance indicator for abnormal results (NCS/CS), description of abnormality -, visit, date, and reason test not performed (if applicable). All visits will be included in the data listing.

13.5.5 Physical examination (PE)

PE will be assessed at screening, treatment week 1, 2, 4, 12, 24, 48. PE data will be listed only for SAF and will include the body system, exam result, clinical significance, description of abnormality, visit, date, and reason test not performed (if applicable). All visits, including screening and unscheduled, will be included in the data listing.

14 PHARMACOKINETICS

14.1 GM-CSF Concentration

Plasma concentrations of GM-CSF [endpoint 7.4] will be summarized at Baseline (pre-dose), post-dose 2h, and at pre-dose and 2h post-dose at Treatment Weeks 2, 12, 24, 36, 48, EOT and at Follow up Weeks 12, 24 by group and overall for PKAS using descriptive statistics including the mean, SD, median, Q1, Q3, min, and max. Concentration values below limit of quantification (BLQ) or less than the limit of quantification (<LLOQ) will be set to 0.

15 FIGURES

15.1 Efficacy

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.

15.2 Safety

All safety figures will graphically present Box Plots summarizing change from baseline values for all regularly scheduled post-baseline visits. These will include both pre-dose and post-dose (or pre-PFT and post-PFT) values when applicable. Laboratory parameters will also be presented in spaghetti plots summarizing individual values for all regularly scheduled visits.

The following parameters will be graphically displayed:

- *Laboratory*: hematology leukocytes, eosinophils, basophils, neutrophils, monocytes, and lymphocytes
- *PFT*: FEV1, FVC, and FEV1/FVC
- *Vital Signs*: HR, SBP, DBP, and BMI
- *ECG*: PR Interval, QRS Interval, QT Interval, QTc Interval, and HR

16 REPORTING CONVENTIONS

The mean, median, Q1, Q3, minimum and maximum will be reported to one more decimal place than the raw value. The standard deviation will be reported to two more decimal places.

Count data will be presented as an integer and percentages will be presented to one decimal place.

17 REFERENCES

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18 LISTING OF TABLES, LISTINGS AND FIGURES

Please see “SAV008-02 SAP V1.0 Mock TLF Shells” document for full list and mock shells for tables, listings, and figures. Minor changes to TLF shells will not necessarily result in an SAP amendment.

19 APPENDICES

19.1 CFQ-R Teen/Adult Version Scoring Instructions

19.1.1 General Scoring Instructions

For ease of interpretation, the questions on the CFQ-R are labeled according to the number on the questionnaire and the domain they are designed to measure. The domain label precedes the question number. For example, the first question on the questionnaire is designed to measure a physical symptom and its label is "Phys1." The complete labeling for each version of the CFQ-R is presented under the section entitled "Question Labels".

The following scoring codes were written to be used with CFQ-R data that was entered into a database/spreadsheet where each question is a unique variable. The variable names should match the question labels listed in the "Question Labels" section. Values for each question range from 1 to 4. For questions with responses listed horizontally (left to right) the left response category should be assigned a value of 1, the second category should be assigned a 2, the third a 3, and the rightmost category should be assigned a 4.

Here is an example.

1. Performing vigorous activities such as running or playing sports……. 1 2 3 4

For questions that are listed vertically (top to bottom), the top category should be assigned a value of 1, the next a 2, the third a 3, and the bottom category a 4.

Here is an example.

13. To what extent do you have difficulty walking? Scoring Values

1. You can walk a long time without getting tired (1)
2. You can walk a long time, but you get tired (2)
3. You cannot walk a long time because you get tired quickly (3)
4. You avoid walking whenever possible because it's too tiring for you (4)

It is important that you assign the values according to these rules for each question. Some of the questions will be phrased in a positive direction (like Question 13 listed above) and the values may seem inappropriate. The scoring codes reverse the ordering for these positively phrased questions. **Do not reverse the coding when you are entering the scores into your database/spreadsheet.** We have found it to be more accurate to let the scoring procedures address the reverse coding.

Please note that question 43 (resp43) on the Teen/Adult version and question 37 (resp37) on the Parent version have one extra category (don't know) we typically assign a value of 5 to that category. This question is not included in the scoring of the respiratory scale.

19.1.2 SAS Program Codes for Scoring the CFQ-R Teen/Adult Version

```
/*This scoring program requires that the data be imported into a SAS table
titled "CFQR_TA" and that the variable names in the table match those listed
below.*/

Data CFQR_TA; set CFQR_TA;

/* Recoding Some Variables */

vital6      =     5-vital6;
vital10     =     5-vital10;
phys13      =     5-phys13;
treat15     =     5-treat15;
treat17     =     5-treat17;
health18    =     5-health18;
social23    =     5-social23;
social28    =     5-social28;
social30    =     5-social30;
health32    =     5-health32;
health34    =     5-health34;
role35      =     5-role35;
resp43      =     5-resp43;

/* Calculating Scores */

if nmiss (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20) <= 4
then
physical = (mean (phys1, phys2, phys3, phys4, phys5, phys13, phys19,
phys20)-1)/3*100;

if nmiss (role35, role36, role37, role38) <= 2 then
role = (mean (role35, role36, role37, role38)-1)/3*100;

if nmiss (vital6, vital9, vital10, vital11) <= 2 then
vitality = (mean (vital6, vital9, vital10, vital11)-1)/3*100;

if nmiss (emot7, emot8, emot12, emot31, emot33) <= 2 then
emotion = (mean (emot7, emot8, emot12, emot31, emot33)-1)/3*100;

if nmiss (social22, social23, social27, social28, social29, social30) <= 3
then
social = (mean (social22, social23, social27, social28, social29, social30)-
1)/3*100;

if nmiss (body24, body25, body26) <= 1 then
body = (mean (body24, body25, body26)-1)/3*100;
```

```
if nmiss (eat14, eat21, eat50) <= 1 then
eat = (mean (eat14, eat21, eat50)-1)/3*100;

if nmiss (treat15, treat16, treat17) <= 1 then
treat = (mean (treat15, treat16, treat17)-1)/3*100;

if nmiss (health18, health32, health34) <= 1 then
health = (mean (health18, health32, health34)-1)/3*100;

if nmiss (weight39) = 0 then
weight= (mean (weight39)-1)/3*100;

if nmiss (resp40, resp41, resp42, resp44, resp45, resp46) <= 3 then
respirat = (mean (resp40, resp41, resp42, resp44, resp45, resp46)-1)/3*100;

if nmiss (digest47, digest48, digest49) <= 1 then
digest = (mean (digest47, digest48, digest49)-1)/3*100;
run;
```

19.2 Pulmonary Exacerbation MedDRA Search List

MedDRA term	MedDRA code	MedDRA level (qualifier)
Infective pulmonary exacerbation of cystic fibrosis	10070608	PT

19.3 Anti-Mycobacterial Medication WHO Drug Dictionary Search List

WHO Drug term	WHO Drug code	WHO Drug level (qualifier)
AMIKACIN	00391001001	PT
AZITHROMYCIN	00944301001	PT
CEFOXITIN	00454701001	PT
CLARITHROMYCIN	00984601001	PT
CLOFAZIMINE	00224701001	PT
CO-TRIMOXAZOLE	13286701802	PT
ETHAMBUTOL	00022301001	PT
IMIPENEM	00788801001	PT
LINEZOLID	01436301001	PT
MOXIFLOXACIN	01453201001	PT
MINOCYCLINE	00232401001	PT
RIFAMPICIN	00146901005	PT
RIFABUTIN	851201001	PT
STREPTOMYCIN	00051001001	PT
TIGECYCLINE	05505301002	PT