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CLINICAL TRIAL PROTOCOL

A Randomised, Double-Blind, Placebo-Controlled Multicentre Clinical Trial of Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis Patients
“IMPALA”

Trial code:	MOL-PAP-002	Trial development phase:	II/III
EudraCT number:	2015-003878-33	Investigational medicinal product:	Molgramostim nebuliser solution
		Indication:	Autoimmune pulmonary alveolar proteinosis
Version:	5.0	Date:	01 Dec 2017
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Simon Day, PhD
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Clinical Trials Consulting and Training
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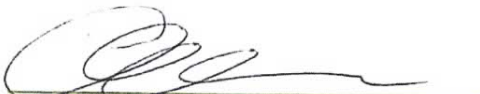
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1 SYNOPSIS

Name of the Sponsor/Company: Savara ApS	Trial Code: MOL-PAP-002
Name of Investigational Medicinal Product: Molgramostim nebuliser solution	EudraCT No.: 2015-003878-33
Development Phase of the Trial: II/III	Trial under an IND: No
TITLE OF THE TRIAL: A randomised, double-blind, placebo-controlled multicentre clinical trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis patients	
OBJECTIVES:	
<i>Primary objective:</i>	
<ul style="list-style-type: none"> To compare efficacy of inhaled molgramostim on the Alveolar-arterial oxygen difference ((A-a)DO₂) with placebo after 24-weeks treatment. 	
<i>Key Secondary objectives:</i>	
<ul style="list-style-type: none"> To compare efficacy of inhaled molgramostim on tolerance to exercise with placebo after 24-weeks of treatment To compare efficacy of inhaled molgramostim on respiratory disease-related quality of life with placebo after 24-weeks of treatment To compare efficacy of inhaled molgramostim based on time to Whole Lung Lavage (WLL) with placebo during 24-weeks of treatment. To compare safety of inhaled molgramostim with placebo in terms of reported adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), severe AEs and withdrawals due to AEs during 24-weeks treatment 	
<i>Further Secondary objectives:</i>	
<ul style="list-style-type: none"> To compare efficacy of inhaled molgramostim on Vital Capacity (VC), Diffusion Capacity of the Lung for Carbon Monoxide (DLCO), Forced Expiratory Volume in one (1) second (FEV₁), Forced Vital Capacity (FVC) and Arterial oxygen tension (PaO₂) with placebo after 24-weeks treatment To compare efficacy of inhaled molgramostim on the categorical change of (A-a)DO₂, VC, DLCO, FEV₁, FVC, and PaO₂ with placebo after 24-weeks treatment To compare efficacy of inhaled molgramostim on categorical change in tolerance to exercise with placebo after 24-weeks treatment To compare efficacy of inhaled molgramostim on dyspnoea, and cough with placebo after 24-weeks treatment To compare efficacy of inhaled molgramostim on disease severity by Computer Tomography (CT) scoring with placebo after 24-weeks treatment 	

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Development Phase of the Trial: II/III	Trial under an IND: No
<p><i>Exploratory objectives:</i></p> <p><i>Double-blind treatment period</i></p> <ul style="list-style-type: none"> To compare efficacy of inhaled molgramostim with placebo on (A-a)DO₂, VC, DLCO, FEV₁, FVC, PaO₂, and on tolerance to exercise after 4-weeks and 12-weeks treatment To compare the duration of response of inhaled molgramostim with placebo in (A-a)DO₂ and tolerance to exercise To compare efficacy of inhaled molgramostim with placebo on dyspnoea and cough after 4-weeks, and 12-weeks treatment To compare efficacy of inhaled molgramostim with placebo on Quality of Life (QoL) after 4-weeks, 12-weeks, and 24-weeks treatment To assess pharmacodynamic effects on selected biomarkers in serum after 4-weeks, 12-weeks, and 24-weeks treatment of inhaled molgramostim or placebo To assess the effect of molgramostim on Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) concentration in serum after the first dose and after 4-weeks treatment, and to assess levels of antibodies to GM-CSF (anti-GM-CSF) after 4-weeks, 12-weeks and 24-weeks treatment with molgramostim or placebo To assess the requirement for oxygen supplementation therapy during 24-weeks treatment with molgramostim or placebo To assess the change in Disease Severity Score (DSS) from Screening to Week 24 <p><i>Follow-up period</i></p> <ul style="list-style-type: none"> To compare the requirement for and time to WLL, or other treatment for autoimmune Pulmonary Alveolar Proteinosis (aPAP) after 24-weeks inhaled molgramostim or placebo during a 24-week or 48-week post-treatment Follow-up period To compare efficacy of 24-weeks inhaled molgramostim with placebo on (A-a)DO₂, VC, DLCO, FEV₁, FVC, PaO₂, and on tolerance to exercise during a 24-week or 48-week post-treatment Follow-up period To compare safety of inhaled molgramostim with placebo during a 24-week or 48-week post-treatment Follow-up period in terms of reported AEs, severe AEs, SAEs, and ADRs To assess levels of anti-GM-CSF at the 12-weeks and 24-weeks post-treatment Follow-up visits To assess the change in DSS during a 24-week or 48-week post-treatment Follow-up period 	

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Development Phase of the Trial: II/III	Trial under an IND: No
OVERALL TRIAL DESIGN: <p>A Screening Visit will be conducted 14 days (± 7 days) prior to the Baseline Visit to determine eligibility. Subjects with aPAP confirmed to be stable or progressive during a period of at least two months prior to the Baseline Visit will be eligible for treatment. Subjects are not eligible for treatment if spontaneous remission has occurred during this 2-month period, defined as absolute VC improved by more than 5% and/or DLCO improved by more than 10%.</p> <p>At the Baseline Visit, eligible subjects will be randomised to receive treatment for up to 24 weeks with either:</p> <ol style="list-style-type: none">1) inhaled molgramostim (300 μg) administered once daily,2) inhaled molgramostim (300 μg) and matching placebo administered intermittently (12 cycles of seven days molgramostim, seven days placebo; both administered once daily) or3) inhaled placebo administered once daily. <p>The trial will include two phases; a Double-blind treatment period consisting of up to eight trial visits (Screening, Baseline, and at Weeks 4,8,12, 16, 20 and 24 after randomisation) and a Follow-up period consisting of up to five trial visits (at Weeks 4, 12, 24, 36 and 48 post-treatment). The 36 and 48-weeks post-treatment visits will only be applicable to subjects included before amendment 11 to the protocol was approved by the national authorities. Participating subjects will be encouraged to contact the clinic between visits if they experience AEs or have any concerns.</p> <p>Subjects completing the 24-week Double-blind treatment period will enter a 24-week or 48-week Follow-up period and will receive treatment with inhaled molgramostim (300 μg) administered once daily in an intermittent regimen (12 or 24) cycles of seven days molgramostim, seven days off).</p> <p>During the trial, WLL will be applied as rescue therapy. The criterion for performing WLL is clinical worsening of aPAP based on symptoms, reduced exercise capacity and/or findings of hypoxemia or desaturation according to the Investigator's judgement. The reason(s) for conducting WLL will be documented. Subjects undergoing WLL during the Double-blind treatment period will continue double-blind trial treatment. Treatment with molgramostim in the Follow-up period should be discontinued in case of disease worsening and/or safety concerns.</p> <p>After completion of both the Double-blind and Follow-up trial periods, subjects who require further treatment will be offered treatment with molgramostim in a Compassionate Use Programme, where national regulations so allow.</p>	
INVESTIGATIONAL MEDICINAL PRODUCT: <i>Investigational Medicinal Product (IMP):</i> Molgramostim nebuliser solution <i>Active Substance:</i> Molgramostim, recombinant human Granulocyte Macrophage Colony Stimulating Factor (rhGM-CSF) <i>Pharmaceutical form:</i> Nebuliser solution <i>Route of administration:</i> Inhalation <i>Inhalation device:</i> PARI eFlow (PARI Pharma GmbH)	

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Development Phase of the Trial: II/III	Trial under an IND: No
NUMBER OF SUBJECTS: 90 subjects (30 in each treatment group) are intended to be randomized. The sample size calculation for the primary endpoint was based on data in an earlier trial, where the mean (and standard deviation) (A-a)DO ₂ were 31.3 (7.4) before treatment and 12.9 (7.6) after treatment (all measured in mmHg). It was also based on previous assumptions about how the trial would be analysed (notably, to combine the two active doses together for the primary analysis). The sample size calculation based on an unpaired t-test of mean difference between the two active arms (combined) vs. placebo, using a significance level of 0.01 and a power of 90% and a delta of 10 mmH, resulted in a required number of 42 subjects, 14 in each treatment arm. Based on an evaluation of variability and plausible effect sizes for the key secondary endpoints, the sample size is increased to 90 subjects (30 patients in each treatment arm), to increase the power to identify statistically significant treatment effects also on one or more of the key secondary endpoints. A fully blinded sample size re-estimation procedure will be carried out in January 2018 for the key secondary endpoints to assess the standard deviations of the 6 Minute Walk Distance (6MWD) and the St. George's Respiratory Questionnaire (SGRQ), as well as the overall WLL event rate. If the maximum of these sample size calculations comes to no more than 33 patients per group, then no change to the target sample size will be made. Otherwise, the sample size will be increased to attain 90% power for at least 2 of the 3 key secondary endpoints, subject to the total trial size not exceeding 150 patients.	
NUMBER OF TRIAL CENTRES: An appropriate number of specialised sites in (including but not limited to) Europe (United Kingdom, Denmark, Germany, Italy, France, Greece, Switzerland, Spain, Slovakia, Poland, Portugal, Romania and Netherlands), Turkey, Russia, Israel, Japan, South Korea, Australia, and the United States, will be included.	

MAIN INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria:

- aPAP diagnosed by CT, or by biopsy, or by Broncho Alveolar Lavage (BAL), and by increased GM-CSF autoantibodies in serum
- Stable or progressive aPAP (i.e. absolute VC not improved by more than 5% and/or DLCO not improved by more than 10% - assessed from medical records) during a minimum period of two months prior to the Baseline visit
- PaO₂ <75 mmHg/<10 kPa at rest, OR desaturation of >4 percentage points on the 6 Minute Walk Test (6MWT)
- An (A-a)DO₂ of minimum 25 mmHg/3.33 kPa
- Female or male ≥18 years of age
- Females who have been post-menopausal for >1 year or females of childbearing potential after a confirmed menstrual period using a highly efficient method of contraception (i.e. a method with <1% failure rate such as combined hormonal contraception, progesterone-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, sexual abstinence), during and until 30 days after last dose of trial treatment. Females of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at dosing at Baseline (Visit 2) and must not be lactating
- Males agreeing to use condoms during and until 30 days after last dose of trial treatment, or males having a female partner who is using adequate contraception as described above
- Willing and able to provide signed informed consent
- 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:

- Diagnosis of hereditary or secondary pulmonary alveolar proteinosis (PAP)
- WLL within one month of Baseline
- Treatment with GM-CSF within three months of Baseline
- Treatment with rituximab within six months of Baseline
- Treatment with plasmapheresis within three months of Baseline
- Treatment with any investigational medicinal product within four weeks of Screening
- Concomitant use of sputum modifying drugs such as carbocystein or ambroxol
- History of allergic reactions to GM-CSF
- Connective tissue disease, inflammatory bowel disease or other autoimmune disorder requiring treatment associated with significant immunosuppression, e.g. more than 10 mg/day systemic prednisolone
- Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product
- History of, or present, myeloproliferative disease or leukaemia
- Known active infection (viral, bacterial, fungal or mycobacterial)
- Apparent pre-existing concurrent pulmonary fibrosis
- Any other serious medical condition which in the opinion of the investigator would make the subject unsuitable for the trial

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Development Phase of the Trial: II/III	Trial under an IND: No
<p>ENDPOINTS:</p> <p>Endpoint assessments</p> <p><i>Lung function variables</i> – will be assessed in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force: Standardisation of lung function testing</p> <p><i>CT</i> – A blinded independent assessor will examine the scans and grade the individual subjects improvement as: Improved / Worsened / No change / Data missing – impossible to evaluate</p> <p><i>QoL score</i> – St Georges Respiratory Questionnaire (SGRQ) and EuroQoL-5D (EQ-5D-5L)</p> <p><i>Dyspnoea score</i> – Borg CR10 Scale for dyspnoea (BDS)</p> <p><i>Cough scores</i> – Cough Questions (CQ)</p> <p><i>6MWT</i>– will be performed in accordance with ATS/ERS guidance</p> <p><i>Laboratory analyses</i> – Central and local laboratory will be used for analysis. Analysis of anti-drug antibodies and neutralising antibodies to molgramostim, and anti-drug antibodies to polyethylene glycol (PEG) and recombinant human albumin (rHA) during the trial period will be performed using Good Laboratory Practice (GLP)-validated methods</p> <p>Primary endpoint</p> <ul style="list-style-type: none"> • Absolute change from baseline of (A-a)DO₂ after 24-weeks treatment <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Change from baseline in 6MWD after 24-weeks treatment • Change from baseline in SGRQ total score after 24-weeks treatment • Time to WLL during 24-weeks treatment • Number of AEs, SAEs, ADRs, severe AEs and AEs leading to treatment discontinuation, including clinically significant changes in laboratory tests and electrocardiogram (ECG) variables, during 24-weeks treatment <p>Further Secondary Endpoints:</p> <ul style="list-style-type: none"> • Absolute change from baseline in VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), FVC (% predicted) and relative change from baseline in PaO₂ after 24-weeks treatment • Number of subjects with >5 mmHg/>0.67 kPa and number of subjects with >10 mmHg/>1.33 kPa improvement in (A-a)DO₂ after 24-weeks treatment • Number of subjects with >5 percentage points and number of subjects with >10 percentage points improvement in VC (% predicted) after 24-weeks treatment • Number of subjects with >10 percentage points improvement in DLCO (% predicted) after 24-weeks treatment 	

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<ul style="list-style-type: none"> • Number of subjects with >10 percentage points improvement in FEV₁ (% predicted) and FVC (% predicted) after 24-weeks treatment • Number of subjects with >10% relative improvement in PaO₂ after 24-weeks treatment • Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 24-weeks treatment • Change from baseline in dyspnoea score and cough scores after 24-weeks treatment • Number of subjects with improved CT score after 24-weeks treatment 	
<p>Exploratory Endpoints</p> <p><i>Double-blind treatment period</i></p> <ul style="list-style-type: none"> • Absolute change from baseline of (A-a)DO₂, VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), FVC (% predicted), and relative change from baseline of PaO₂ after 4 and 12-weeks treatment • Time period during which the (A-a)DO₂ level is maintained below Baseline –10mmHg • Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 4 and 12-weeks treatment • Time period during which the improvement in tolerance to exercise is maintained • Change from baseline in dyspnoea score and cough scores after 4 and 12-weeks treatment • Number of subjects with improved QoL (change of ≥4 units on the SGRQ/number of subjects with 'no problems' in EQ-5D-5L), after 4, 12, and 24-weeks treatment • Change in serum concentration of biomarkers: Krebs von den Lungen-6 (KL-6), Carcinoembryonic antigen (CEA), Surfactant Protein A (SP-A), Surfactant Protein B (SP-B), Surfactant Protein C (SP-C), Surfactant Protein D (SP-D), Cytokeratin 19 Fragment (Cyfra 21-1) and Lactate Dehydrogenase (LDH) after 4, 12, and 24-weeks treatment • Levels of antibodies towards Granulocyte Macrophage Colony Stimulating Factor (anti-GM-CSF) after 4, 12 and 24-weeks treatment • Change in serum concentration of GM-CSF post first dose of trial drug and after 4-weeks of treatment • Number of subjects in need for oxygen supplement therapy during 24-weeks treatment • The distribution of DSS at Screening and at Week 24 • The percentage of subjects with DSS 1 or 2 at Screening and at Week 24 <p><i>Follow-up period</i></p> <ul style="list-style-type: none"> • Number of subjects requiring WLL, or other treatment for aPAP and number of treatment courses required during 24-weeks or 48-weeks follow-up • Time to WLL, or other treatment for aPAP during 24-weeks or 48-weeks follow-up 	

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<ul style="list-style-type: none"> • Absolute change from baseline in (A-a)DO₂ and VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), FVC (% predicted), and relative change from baseline of PaO₂ after 12, 24, 36 and 48-weeks follow-up • Number of subjects with improved tolerance to exercise (increase in distance walked \geq50 m or desaturation $<$4 percentage points on the 6MWT) after 12, 24, 36 and 48-weeks follow-up • Number of AEs, severe AEs, SAEs and ADRs, including clinically significant changes in laboratory tests and ECG variables, during 24-weeks or 48-weeks follow-up • Levels of anti-GM-CSF, after 12 and 24 weeks follow-up • The distribution of DSS after 24 and 48-weeks follow-up • The percentage of subjects with DSS 1 or 2 after 24 and 48-weeks follow-up 	
<p>STATISTICAL METHODS:</p> <p>The trial will be unblinded and primary analysis will be conducted after the 24 week Double-blind treatment period.</p> <p>The primary efficacy variable, (A-a)DO₂, will be tested using an analysis of covariance (ANCOVA) model. This model will have change from baseline to Week 24 in (A-a)DO₂ as the response variable, whilst treatment group and baseline (A-a)DO₂ will be predictor variables. The mean difference between each active dose and placebo in change from baseline of (A-a)DO₂ will be estimated, along with its 95% confidence interval (CI) and associated statistical significance test.</p> <p>The key secondary endpoints of change from baseline in 6MWD and in SGRQ will be analysed using the same ANCOVA model as for (A-a)DO₂. Time to WLL will be analysed by logrank test.</p> <p>Comparisons (for the primary and key secondary endpoints) will be carried out as follows. The first will be of once daily dosing vs. placebo, and the second will be of intermittent dosing vs. placebo. These comparisons will be made in sequence: the once daily dosing group will first be compared with placebo for the primary endpoint and, if significant at P$<$0.05, then the 3 key secondary endpoints will be tested at an overall 5% significance level using the Hochberg procedure. If the test is significant for all of the key secondary endpoints, then the hierarchical testing will proceed with comparing intermittent dosing vs. placebo for the primary, and then the key secondary, endpoints in the same manner as for once daily dosing vs. Placebo.</p> <p>Subjects who withdraw early will have (A-a)DO₂ measurement values imputed by multiple imputation used as their endpoint. Sensitivity analyses will be described in the Statistical Analysis Plan (SAP).</p> <p>Analyses pertaining to the Further Secondary Endpoints will be described in the SAP.</p> <p>Data from the Follow-up period will be reported descriptively in a separate Follow-up report.</p>	
<p>TRIAL PERIOD:</p> <p>The duration of trial participation for each subject is approximately 50 to 78 weeks:</p> <ul style="list-style-type: none"> • Screening period for the subjects is 14 days (+/- 7 days) • Double-blind period up to 24 weeks (+/- 7 days) • Open-label period for 24 or 48 weeks (+/- 14 days) 	

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 List of Abbreviations

6MWD	6 Minute Walk Distance
6MWT	6 Minute Walk Test
(A-a)DO ₂	Alveolar-arterial Oxygen Difference
ANCOVA	Analysis of Covariance
aPAP	Autoimmune Pulmonary Alveolar Proteinosis
ADR	Adverse Drug Reaction
AE	Adverse Event
anti-GM-CSF	Antibodies towards Granulocyte Macrophage Colony Stimulating Factor
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area Under the Plasma Concentration vs Time Curve
BAL	Broncho-alveolar Lavage
BALF	Broncho Alveolar Lavage Fluid
BALT	Bronchi-associated Lymphoid Tissue
b.i.d	Bis in die (twice daily)
BDS	Borg CR10 Scale for Dyspnoea
CA	Competent Authority
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
C _{max}	Maximum Plasma Concentration
C _{min}	Minimum Plasma Concentration
CQ	Cough Questions
CT	Computer Tomography
CTR	Clinical Trial Report
Cyfra 21-1	Cytokeratin 19 Fragment
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
DSMB	Data Safety Monitoring Board
DSS	Disease Severity Score
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

eGFR	Estimated Glomerular Filtration Rate
EEA	European Economic Area
eow	Every Other Week
EQ-5D-5L	EuroQol-5D 5 level quality of life questionnaire
ERS	European Respiratory Society
FAS	Full Analysis Set
FDA	Food and Drug Administration
FeNO	Fraction Exhaled of Nitric Oxide
FEV ₁	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMP	Good Manufacturing Practice
HR-CT	High Resolution Computed Tomography
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
KL-6	Krebs von den Lungen-6
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PaO ₂	Arterial oxygen tension
PAP	Pulmonary Alveolar Proteinosis
PAS	Periodic Acid-Schiff
PBPC	Peripheral Blood Progenitor Cells
PCV/EVF	Packed Cell Volume (PCV) or Erythrocyte Volume Fraction (EVF) also known as hematocrit
PPS	Per Protocol Set

PT	Preferred Term
QoL	Quality of Life
rhGM-CSF	Recombinant Human Granulocyte Macrophage Colony Stimulating Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRQ	St Georges Respiratory Questionnaire
SOC	System Organ Class
SOP	Standard Operating Procedure
SP-A, SP-B, SP-C, SP-D	Surfactant Protein A, Surfactant Protein B, Surfactant Protein C, Surfactant Protein D
SpO ₂	Oxygen saturation (indirect measurement)
TLC	Total Lung Capacity
t _{max}	Time of maximum plasma concentration
VC	Vital Capacity
WHO	World Health Organisation
WLL	Whole Lung Lavage

3.2 Definition of Terms

(A-a)DO ₂	Alveolar-arterial oxygen difference is a measure of the difference between the alveolar concentration (A) of oxygen and the arterial (a) concentration of oxygen
DLCO	Uptake of carbon monoxide from a single inspiration in a standard time.
FEV ₁	The volume of air that can forcibly be blown out in one second, after full inspiration.
FVC	The maximum amount of air a person can expel from the lungs after a maximal inhalation and during a forceful expiration.
SpO ₂	Indirect measurement of oxygen saturation using a finger probe, ear sensor or similar device.
6MWD	Distance in meters walked during the 6MWT.
6MWT	Test used to measure the distance that a subject can walk quickly on a flat hard surface in a period of 6 minutes (at an individually predetermined oxygen supplementation).
VC	The maximum amount of air a person can expel from the lungs after a maximum inhalation.

4 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

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5 INTRODUCTION

5.1 Background

Pulmonary alveolar proteinosis (PAP)

Pulmonary alveolar proteinosis (PAP) is a rare autoimmune disease with an estimated prevalence of 0.7 per 100,000 individuals [1]. It is characterised by high levels of autoantibodies against Granulocyte Macrophage Colony Stimulating Factor (auto anti-GM-CSF) in alveoli and blood. The autoantibodies neutralise the normal biologic action of Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) in the lungs [2]. Pulmonary Alveolar Proteinosis is also characterised by the accumulation of Periodic Acid-Schiff (PAS)-positive lipoproteinaceous material, primarily phospholipid surfactant, and surfactant apoproteins in the distal air spaces. Consequently gas transfer is decreased leading to impairment of gas exchange, respiratory failure, and to increased risk of respiratory infections [1,3,4,5]. More than 90% of the reported cases of PAP are classified as the autoimmune disorder type associated with GM-CSF autoantibodies (aPAP). Less common are the secondary and congenital types [4,5].

The clinical presentation for PAP is variable and nonspecific with subacute symptoms of cough, dyspnoea, activity intolerance, occasional chest pain, and general malaise. Although PAP spans all ages, the typical adult PAP patient is aged between 41 and 51 years, and has a history of progressive dyspnoea and cough. Fifty percent of the patients have the above symptoms for less than seven months; another 25% of patients report having symptoms of two years or longer. Up to a third of the PAP cases may be minimally symptomatic [6]. Spirometry evaluation generally shows a restrictive pattern of ventilatory defect; the pulmonary diffusing capacity is reduced, out of proportion with the fall in vital capacity (VC) [7,8,9]. Arterial blood gas analysis shows mild to moderate hypoxaemia, with an elevated alveolar-arterial gradient and elevation in shunt fraction [6,8,10]. Analysis of Broncho Alveolar Lavage Fluid (BALF) may facilitate the diagnosis in clinically suspected cases. The BALF may have a 'milky' appearance, with large amounts of granular, acellular eosinophilic lipoproteinaceous material which is PAS positive [11,12].

No evidence-based curative treatment exists for patients with PAP. There is, therefore, a need for new and modern treatment approaches for PAP patients. Sequential whole lung lavage (WLL) under general anesthesia has become the standard of care. Whole Lung Lavage decreases the symptoms and improves the oxygenation in PAP patients. It is not possible to predict how many WLL treatments a particular patient will need; a single WLL is sufficient for some patients while others require lavage every six to 12 months for many years. The observation that mice deficient in the gene for GM-CSF develop alveolar accumulations of surfactant substances similar to that seen in PAP led to the suggestion of a potential role for recombinant human GM-CSF (rhGM-CSF) in the treatment of PAP [13].

It is generally accepted today that once the disease is diagnosed its outcome appears to be much better compared to old, historical data. Overall disease specific survival rates exceed 80% at five years [14,15].

The most common cause of death is respiratory failure, typically occurring within the first year after diagnosis. Secondary pulmonary infections with bacteria and other organisms occasionally develop due to impaired macrophage function; these infections require extensive treatment.

Investigational Medicinal Product (IMP)

The IMP, Molgramostim nebuliser solution, has initially been developed by Serendex Pharmaceuticals A/S and is now further developed by Savara.

The drug substance molgramostim (rhGM-CSF) is produced in *E. coli* and has the same amino acid sequence as the native protein but is not glycosylated. Another rhGM-CSF

product, sargramostim, which is produced in *S. cerevisiae* slightly differs from native GM-CSF by having one amino acid difference in position 23 and is glycosylated. Production of molgramostim in bacteria circumvents the variability in the molecular weight seen in sargramostim. The formulation currently under development is intended for inhalation use.

Both molgramostim and sargramostim have been approved largely for use following chemotherapy and/or bone marrow transplantation to reduce the risks of neutropenia such as infection or graft rejection. Molgramostim has been marketed in Europe and Australia as Leucomax[®]. However it was discontinued in 2002 for unknown reasons. Sargramostim, as Leukine[®], is currently approved by the US Food and Drug Administration (FDA) for use in five indications at a dose of 250 µg/m² per day using intravenous (IV) and/or subcutaneous administration depending on indication [16]. It is reported by the Marketing Authorisation (MA) holder that approximately 470,000 patients have received Leukine treatment in the post-marketing setting from the time of product launch in March 1991 through December 2012 [17].

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

Increases in incidence or severity of inflammatory cell infiltration, bronchi-associated lymphoid tissue (BALT) hyperplasia, pleural inflammation, and granulomas were similar across animals treated with 42 µg/kg/day and those treated with 127 µg/kg/day, likely due to anti-drug antibodies. These findings were not associated with any clinically impaired respiratory function and in animals sacrificed after a 4-week treatment free period, partial resolution of these findings was noted. Bronchopneumonia was found in one animal treated at each of the two dose levels. While a relationship to the test item cannot be excluded, these findings were likely a consequence of the bronchoalveolar lavage (BAL) procedure, which was conducted pre-treatment and at termination in every animal from this study. This is supported by the fact that no such lesions were detected in monkeys treated with 40 µg/kg/day for 13 weeks in a study that did not include the BAL procedure.

The No Observed Adverse Effect Level (NOAEL) was based on the clinical severity of the bronchopneumonia in the monkey treated with 127 µg/kg/day, as opposed to the incidental histopathologic finding of bronchopneumonia without clinical signs in the animal treated with 42 µg/kg/day, and consequently was set at the 40 µg/kg/day nominal dose level. This was subsequently confirmed by inhalation toxicity studies of longer duration (up to 26 weeks), where no bronchopneumonia was reported and no additional dose-limiting toxicity was observed.

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

The first clinical study with molgramostim nebuliser solution has recently been completed (MOL-001). This was a phase I study to investigate the effects of molgramostim nebuliser solution in healthy adult subjects. The study was a randomised, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in 42 adults non tobacco using male and non-child bearing female subjects. In the SAD part, 18 subjects were

included with four subjects in each of the three SAD dose levels (150 µg, 300 µg and 600 µg) and six receiving placebo. In the MAD part, 24 subjects were included with nine subjects in each of the two MAD dose levels (300 µg or 600 µg) and six receiving placebo once daily for six days.

All 42 subjects enrolled completed the study. GM-CSF was not measurable in serum before study drug administration. In the SAD part, GM-CSF was absorbed into systemic circulation with t_{max} of 2 hours after inhalation of molgramostim nebuliser 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 C_{max} ranged between 9.1 and 41 pg/mL (C_{max} was similar for the 300 and 600 µg dose levels). In the MAD part, despite the short half-life of approximately 4 hours where GM-CSF levels returned to levels below quantification limits after each dose, there was evidence of some accumulation after multiple dosing. C_{max} increased from 32 pg/mL on Day 1 to 90 pg/mL on Day 6 for the 300 µg dose level and from 96 pg/mL to 251 pg/mL from Days 1 to 6 for the 600 µg dose level. Likewise AUC_{last} increased from 97 to 248 pg•h/mL from Days 1 to 6 for the 300 µg dose level and from 350 to 802 pg•h/mL for the 600 µg dose level. Minimum measurable plasma concentrations (C_{min}) on Day 6 were 3.6 and 5.1 pg/mL measured at 8 and 12 hours, respectively for the 300 and 600 µg dose levels.

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

The most common AE was cough, reported for 21/30 (70%) subjects receiving molgramostim nebuliser solution and 8/12 (67%) receiving placebo. The AEs considered treatment-related reported by two or more (>5%) subjects receiving molgramostim nebuliser 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 were no serious adverse events (SAEs), severe AEs, dose-limiting toxicity, or other remarkable findings of clinical concern from review of clinical safety data. Further details are available in the Investigator's Brochure (IB).

Previous experience of inhaled rhGM-CSF in PAP patients

Based on the findings that PAP may be caused by autoantibodies to GM-CSF, off-label administration of subcutaneous and inhaled rhGM-CSF in the marketed formulations (molgramostim and sargramostim) has already been explored in the clinic. The results have indicated that therapy with rhGM-CSF can offer an effective and safe treatment for the patient with aPAP. In a recent meta-analysis, including three subcutaneous studies and two inhalation studies, a 59% pooled response rate was calculated with a higher response observed with inhalation use [2].

The majority of aPAP patients participating in published clinical studies using inhaled rhGM-CSF have been treated with sargramostim (approximately 70 patients). Improved pulmonary function was reported from all studies. In three of the six studies the alveolar-arterial oxygen difference ((A-a)DO₂) has been assessed as a measure of response to

treatment. In one trial of 39 patients, a mean reduction of 12.3 (8.4-16.2) mmHg ($p < 0.001$) was observed in the 35 patients that completed the trial [18]. A reduction of 12.6 mmHg at rest ($p = 0.00003$) and 20 mmHg at exercise from 12 patients was reported in another trial [19] and a recent trial [20] reported a mean decrease of 17.4 mmHg ($p = 0.031$). Patients also experienced improvement in dyspnoea (BDS), exercise tolerance assessed by the 6 Minute Walk Test (6MWT), pulmonary function tests such as Diffusion Capacity of the Lungs for Carbon Monoxide (DLCO), Forced Expiratory Volume (FEV), Forced Vital Capacity (FVC), Total Lung Capacity (TLC), Computer Tomography (CT) scans, and nutritional status. In line with these results there are reports of less need for further WLLs and that patients have been able to come off supplementary oxygen; four out of five patients in one trial did not require any further WLL during the course of the trial and the remaining patient had a diminished need for WLL for six months and then required no further WLL [21]. All five patients were able to discontinue supplemental oxygen. The results from the performed studies indicates an improvement that remains present for more than one year after treatment has been discontinued [18,19].

Molgramostim nebuliser solution has not, as yet, been used in aPAP in the clinical setting. However, data are available from eight aPAP patients in which molgramostim products other than molgramostim nebuliser solution have been administered via inhalation [22, 23, 24, 25]. The treatment duration for all patients was 24 weeks or more. Three different treatment regimens applied; three patients received 250 µg/day every other week for 24 weeks, four patients received 150 µg/day for 24 weeks, and one patient received 300 µg/day every other week for three months, followed by 150 µg/day every other week for six months. In the first trial, a decrease between 17 and 27 mmHg in (A-a)DO₂ was reported for the three patients included [22]. In another trial a decrease in (A-a)DO₂ by more than 10 mmHg was reported in two out of four patients, improved VC and CT score was reported in all four patients and improved DLCO, Medical Research Council (MRC) grade (subjective dyspnoea index) and Krebs von den Lungen- 6 (KL-6) were reported in three out of four patients [23]. After three months treatment every other week with 300 µg/day rhGM-CSF the patient studied by Yu et al 2014 had an arterial oxygen tension (PaO₂) of 68 mmHg on room air as well as significant improvement in chest CT [25].

More details about the clinical studies and case reports using inhaled rhGM-CSF are available in the IB.

This is the first trial sponsored by Savara ApS in which the IMP (molgramostim nebuliser solution) is administered to PAP patients.

5.2 Trial Rationale

Today's standard of care, WLL, does not correct the primary defect in aPAP but provides symptomatic benefit to many patients. Whole Lung Lavage is complex to perform, requires prolonged general anaesthesia, is associated with morbidities. In addition, a single WLL is not effective in all patients. Consequently, there is a need for more effective and less invasive therapies for PAP patients [2].

As outlined above, there is a growing body of evidence indicating that rhGM-CSF (molgramostim and sargramostim) may have a positive impact on lung function and morphology in aPAP patients.

The current trial has been designed to investigate the efficacy and safety of a molgramostim formulation specifically developed for inhalation (molgramostim nebuliser solution) in aPAP patients. The trial design is a randomised, double-blind, parallel group comparison of inhaled molgramostim with placebo. The trial consists of a Double-blind treatment period of up to 24 weeks to determine the comparative efficacy and safety of molgramostim. After the

Double-blind treatment period, patients will enter a post treatment Follow-up period of up to 48 weeks to investigate long term outcomes following double-blind treatment.

The randomised, double-blind, placebo-controlled, parallel-group trial design is a scientifically robust comparative design. The use of a placebo arm controls for the natural course of disease and allows the trial to be powered for statistical significance despite the limited number of patients available.

The primary endpoint is (A-a)DO₂, which has been found to be sensitive to treatment with inhaled rhGM-CSF with a low degree of variability in previous literature. In a phase 2 trial the statistically significant improvement in (A- a)DO₂ was accompanied by statistically significant improvements in dyspnoea, need for oxygen supplement, walking distance and minimal oxygen saturation (SpO₂) on the 6MWT, VC and DLCO [18]. Improvements were also associated with morphologic changes as evidenced by statistically significant correlations between high-resolution CT scores and (A-a)DO₂, PaO₂ and DLCO both before and after treatment.

Whilst (A-a)DO₂ is a calculated biomarker, and thus a surrogate marker for clinical effects, the key secondary endpoints focus on important clinical outcomes such as the need for WLL and the effect of treatment on exercise capacity, respiratory symptoms and quality of life. In order to ensure robust effects on the key secondary endpoints the sample size was further increased. Currently WLL is the standard of care for aPAP patients but the procedure is invasive, and carries a known morbidity to the patient. Potential complications associated with WLL include hypoxaemia, hydropneumothorax, adult respiratory disease syndrome, post-procedure infections and pneumothorax [26]. Therefore, a reduced requirement for WLL would be of benefit for the patient. As the main symptom of aPAP is exercise-induced dyspnoea that may limit the activity level of the patient, the 6 Minute Walk Distance (6MWD) and the total score on SGRQ were chosen as key secondary endpoints, although data on these endpoints in aPAP are still limited. In addition, pulmonary function and disease severity based on HR-CT scoring will be assessed as secondary endpoints.

The patient population to be included in the current trial will be patients with aPAP, which accounts for over 90% of PAP cases. Patients with congenital and secondary PAP will not be included. Congenital PAP is often associated with a receptor defect so these patients would be unlikely to benefit from rhGM-CSF treatment and treating the underlying cause of secondary PAP is usually sufficient to resolve the disease. Diagnosis of PAP will be by either high-resolution computer tomography (HR-CT), by open or transbronchial lung biopsy, or by broncho alveolar lavage (BAL) in accordance with current clinical practice. Increased serum anti-GM-CSF will be required for confirmation of the autoimmune disease type. Patients with aPAP confirmed to be stable or progressive during a period of at least two months prior to Baseline will be eligible for treatment. Patients whose condition is spontaneously improving (defined as absolute VC improved by more than 5% and/or DLCO improved by more than 10%) during a period of at least two months prior to Baseline will be excluded.

The sample size calculation for the primary endpoint required a total of 42 subjects (14 in each treatment group) to be randomised. It was also based on previous assumptions about how the trial would be analysed (notably, to combine the two active doses together for the primary analysis). In order to power the study also to have potential to show effects on the key secondary endpoints, additional sample size calculations were conducted and the sample size was set at 90 subjects. Because of the limited data available, a fully blinded sample size re-estimation procedure will be carried out to assess the standard deviations of both the 6MWD and the SGRQ score, as well as the overall WLL event rate, when approximately 50 subjects will have completed 24-weeks of treatment.

The published rhGM-CSF inhalation studies (mainly sargramostim) in aPAP have utilised many different doses, dosing schedules and nebulisers. Doses used include 150 µg rhGM-CSF daily, 125 µg twice daily (b.i.d), 250 µg daily, and 500 µg b.i.d. [19, 20, 21, 22, 23]. Most studies have employed intermittent treatment, most commonly treatment every other week (eow), or four days on, four days off treatment. Cyclic dosing with seven days on/seven days off was introduced in a phase 1 clinical inhalation trial in oncology [28]. The main reason for this cyclic dosing schedule was to reduce potential pulmonary toxicity and damage to local tissues. Another reason was that data from granulocyte-colony stimulating factor (G-CSF) treatment had shown a peak increase in peripheral blood progenitor cells (PBPC) on Days 4-6 of treatment, with a decrease on Day 7. Subsequently, studies in PAP adopted this or similar cyclic dosing schedules. Dosing schedules used in published inhalation studies include treatment eow for 24 weeks, high and low dose cycles with treatment eow for 24 weeks, four treatment days followed by four rest days for six months or more [21], more than eight months with two weeks on/two weeks off treatment, and eow for up to 32 weeks (up to 64 weeks in a single patient) [18,19,21,29,30].

Due to the wide range of dose regimens used, two different dose regimens of molgramostim will be investigated in the current trial. One regimen will be continuous administration of molgramostim 300 µg once daily for 24 weeks and the other regimen will be intermittent administration (12 cycles of seven days molgramostim 300 µg, seven days placebo; both administered once daily). The placebo group will receive continuous daily treatment. Most studies have employed a treatment duration of at least 24 weeks. The time to maximum response with respect to gas exchange has been found to be 24 weeks and a lag time of 4-12 weeks until efficacy is seen has been reported [1,19]. Therefore, the proposed treatment duration of 24 weeks is expected to be sufficient to obtain optimal responses.

The dose estimation for molgramostim is mainly based on the two largest studies [18, 19], which were conducted with sargramostim (only limited data are available for molgramostim). Both studies reported the percentage of responders in terms of improvement of at least 10-12 mmHg in (A-a)DO₂. The percentage of responders was 62% with a daily dose of 250 µg for 12 weeks, followed by 125 µg for 12 weeks [18] and >90% with a daily dose of 500 µg [19]. The responder rates were supported by the changes from baseline in gas exchange and pulmonary function parameters. There were no signs of dose-related toxicity in these studies.

Based on these data with sargramostim, possible differences in biological activity and the nebuliser used must be taken into account when selecting an appropriate dose of molgramostim. *In vitro data* indicated a potency difference between the two compounds of 0.6-0.8 [31, 32], thus a dose of 300 µg molgramostim has been chosen. This dose approximately corresponds to the higher, more effective dose of 500 µg sargramostim. The PARI eFlow nebuliser system which has been found to be a suitable device to administer the molgramostim will be used. Further details are available in the IB.

After completion of the double-blind treatment period, subjects will be assigned to an open-label treatment Follow-up period of 24-weeks or 48-weeks to collect long term outcomes following rhGM-CSF treatment. All subjects who complete the 24-week Double-blind treatment period (regardless of whether they completed trial treatment or discontinued trial treatment prematurely) will enter the open-label period so that as much information as possible can be collected regarding the use of molgramostim in this rare disease. During the open-label Follow-up period subjects will be treated with molgramostim 300 µg daily in an intermittent regimen of 7 days on- and 7 days off-treatment. The data from the open-label Follow-up period will be analysed descriptively and reported separately.

5.3 Potential Risks and Benefits

Currently, no evidence-based curative treatment exists for aPAP. Successive WLL procedures remain the standard treatment without a targeted pathophysiological approach. WLL is an intervention which carries a high morbidity, treats only symptoms, and is not always successful. Due to the pathophysiology of aPAP, this condition can lead to complications, including respiratory infections, pulmonary fibrosis and potentially premature death.

There is currently no approved pharmacological treatment for patients with PAP, and therefore an unmet need for further treatment modalities exists.

Experience with inhaled rhGM-CSF worldwide has demonstrated a reduction in symptoms and improvement in exercise tolerance and objective lung function tests, reducing or eliminating further WLL episodes. Thus treatment with rhGM-CSF has the potential to alter the natural history of PAP [14, 33].

Clinical studies and case reports thus far have indicated the use of inhaled rhGM-CSF to be a well-tolerated, effective and localised treatment that may offer clinical benefits for the great majority of patients, including clearance of excess surfactant-related lipoproteins and prevention of secondary infections [24, 26].

Patients with aPAP have been treated with up to 500 µg of inhaled rhGM-CSF for up to a year [21, 30, 34, 35]. There have been no reports of chronic toxic effects [19].

Results from pre-clinical studies with inhaled molgramostim nebuliser solution showed the expected pharmacological effects on WBC populations locally and systemically in line with observed effects after IV administration of molgramostim. No severe, serious or dose-limiting AEs were observed in the first clinical study in humans (MOL-001). The most common AE was cough, which was reported at a similar incidence for the molgramostim nebuliser solution and placebo. Increases of WBC populations in the blood consistent with the known mechanism of action were observed; most of which were considered not clinically significant. Only two cases (total white blood cell increased and eosinophilia) were reported as AEs. No development of anti-drug antibodies was observed.

Based on information from similar products, the potential dose-limiting toxicity of molgramostim would be based on pulmonary effects, such as bronchoconstriction, dyspnoea, cough or decreased pulmonary function. Pulmonary function and respiratory symptoms will be monitored during the trial and double-blind trial treatment should be discontinued if significant worsening occurs. If there is significant systemic exposure, haematologic findings such as leucocytosis and neutrophilia may occur. Therefore, laboratory safety monitoring will be conducted during the Double-blind treatment period. As non-clinical data on similar products indicate that systemic exposure to rhGM-CSF may be associated with increased pre- and post-implantation losses, pregnancy testing will be performed in women of childbearing potential prior to dosing, at monthly intervals during the Double-blind treatment period and the open-label treatment Follow-up period.

Treatment with molgramostim nebuliser solution is expected to be more effective, less invasive, and more convenient, than the currently available symptomatic treatment, WLL, for patients with aPAP. In the current trial two thirds of the subjects will receive active drug and one third will receive placebo. Rescue treatment with WLL will be available for all subjects who experience any unacceptable lack of response or disease progression during the trial. Subjects requiring WLL during the Double-blind treatment period will continue trial treatment.

6 TRIAL OBJECTIVES

6.1 Primary Objective

The primary objective is:

- To compare efficacy of inhaled molgramostim on the Alveolar-arterial oxygen difference ((A-a)DO₂) with placebo after 24-weeks treatment

6.2 Secondary Objectives

6.2.1 Key Secondary objectives:

- To compare efficacy of inhaled molgramostim on tolerance to exercise with placebo after 24-weeks of treatment
- To compare efficacy of inhaled molgramostim on respiratory disease-related quality of life with placebo after 24-weeks of treatment
- To compare efficacy of inhaled molgramostim based on time to Whole Lung Lavage (WLL) with placebo after 24-weeks treatment
- To compare safety of inhaled molgramostim with placebo in terms of reported adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), severe AEs and withdrawals due to AEs during 24-weeks treatment.

6.2.2 Further Secondary objectives:

- To compare efficacy of inhaled molgramostim on Vital Capacity (VC), Diffusion Capacity of the Lung for Carbon Monoxide (DLCO), Forced Expiratory Volume in one second (FEV₁), Forced Vital Capacity (FVC) and Arterial oxygen tension (PaO₂) with placebo after 24-weeks treatment
- To compare efficacy of inhaled molgramostim on the categorical change of (A-a)DO₂, VC, DLCO, FEV₁, and PaO₂ with placebo after 24-weeks treatment
- To compare efficacy of inhaled molgramostim on categorical change in tolerance to exercise with placebo after 24-weeks treatment
- To compare efficacy of inhaled molgramostim on dyspnoea, and cough with placebo after 24-weeks treatment
- To compare efficacy of inhaled molgramostim on disease severity by Computer Tomography (CT) scoring with placebo after 24-weeks treatment

6.3 Exploratory Objectives

6.3.1 Double-blind treatment period

- To compare efficacy of inhaled molgramostim with placebo on (A-a)DO₂, VC, DLCO, FEV₁, PaO₂, and on tolerance to exercise after 4-weeks and 12-weeks treatment
- To compare the duration of response of inhaled molgramostim with placebo in (A-a)DO₂ and tolerance to exercise
- To compare efficacy of inhaled molgramostim with placebo on dyspnoea and cough after 4-weeks, and 12-weeks treatment
- To compare efficacy of inhaled molgramostim with placebo on Quality of Life (QoL) after 4-weeks, 12-weeks, and 24-weeks treatment

- To assess pharmacodynamic effects on selected biomarkers in serum after 4-weeks, 12-weeks, and 24-weeks treatment of inhaled molgramostim or placebo
- To assess effect of molgramostim on Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) concentration in serum after the first dose and after 4-weeks treatment and to assess levels of antibodies to GM-CSF after 4-weeks, 12-weeks and 24-weeks treatment with molgramostim or placebo
- To assess the requirement for oxygen supplementation therapy during 24-weeks treatment with molgramostim or placebo
- To assess the change in Disease Severity Score (DSS) from Screening to Week 24

6.3.2 Follow-up period

- To compare the requirement for and time to WLL, or other treatment for aPAP after 24-weeks inhaled molgramostim or placebo during a 24-week or 48-week post-treatment Follow-up period
- To compare efficacy of 24-weeks inhaled molgramostim with placebo on (A-a)DO₂, VC, DLCO, FEV₁, PaO₂, and on tolerance to exercise during a 24-week or 48-week post-treatment Follow-up period
- To compare safety of inhaled molgramostim with placebo during a 24-week or 48-week post-treatment Follow-up period in terms of reported AEs, severe AEs, SAEs, and ADRs
- To assess levels of antibodies to GM-CSF at 12-weeks and 24-weeks post-treatment with molgramostim or placebo
- To assess the change in DSS during a 24-week or 48-week post-treatment Follow-up period

7 INVESTIGATIONAL PLAN

7.1 Trial Design and Plan-Description

A Screening Visit will be conducted 14 days (± 7 days) prior to the Baseline Visit to determine eligibility. Subjects with aPAP confirmed to be stable or progressive during a period of at least two months prior to the Baseline Visit will be eligible for treatment. Subjects are not eligible for treatment if spontaneous remission has occurred during this two-month period, defined as absolute VC improved by more than 5% and/or DLCO improved by more than 10%.

At the Baseline Visit, eligible subjects will be randomised to receive treatment for up to 24 weeks with either:

- 1) inhaled molgramostim (300 μg) administered once daily,
- 2) inhaled molgramostim (300 μg) and matching placebo administered intermittently (12 cycles of seven days molgramostim, seven days placebo; both administered once daily) or
- 3) inhaled placebo administered once daily.

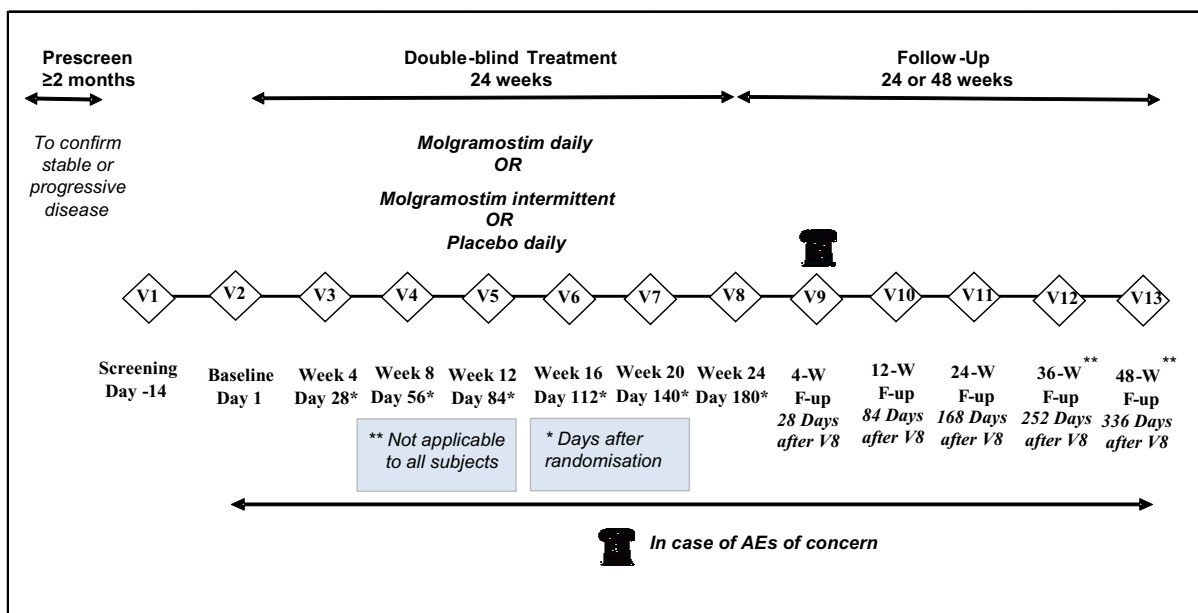
The trial will include two phases; a Double-blind treatment period consisting of up to eight trial visits (Screening, Baseline, and at Weeks 4, 8, 12, 16, 20 and 24 after randomisation) and an open-label treatment Follow-up period consisting of up to five trial visits (at Weeks 4, 12, 24, 36 and 48 post-treatment). The 36 and 48-weeks post treatment visits are only applicable for subjects included before amendment 11 to the protocol was approved by the national authorities in the country where the subject originates from.

Participating subjects will be encouraged to contact the clinic between visits if they experience AEs or have any concerns (*Figure 1*).

During the trial, WLL will be applied as rescue therapy. The criterion for performing WLL is clinical worsening of aPAP based on symptoms, reduced exercise capacity and/or findings of hypoxemia or desaturation according to the Investigator's judgement. The reason(s) for conducting WLL will be documented. Subjects undergoing WLL during the Double-blind treatment period will continue double-blind trial treatment. All subjects completing the 24-week Double-blind treatment period will enter a 24- or 48-weeks Follow-up period and will receive open-label treatment with inhaled molgramostim 300 μg daily for 7 days, followed by 7 days off-treatment. This cycle will be repeated for 12 or 24 weeks depending on when the subject is enrolled in the trial. Open-label treatment in the last 24 weeks of the Follow-up period is not mandatory for subjects who have entered this period before amendment 11 was approved by the national authorities.

After completion of both the Double-blind treatment and Follow-up trial periods, subjects who require further treatment will be offered treatment with molgramostim in a Compassionate Use Programme, where national regulations so allow.

Figure 1 Overall Trial Design



7.2 Trial Procedures

7.2.1 Schedule of Trial Events

The trial assessments described in the sections below are presented in detail in *Section 10.1* (Efficacy assessments), *Section 10.3* (Demographic data and Other Baseline characteristics) and *Section 10.4* (Safety assessments). Recording and reporting of AEs are described in detail in *Section 11*.

The timing of all trial events is shown in *Table 1* in *Section 7.2.2*.

7.2.1.1 Pre-Screening Visit Period

Only applicable to trial sites that do not analyse anti-GM-CSF using a validated quantitative measurement as routine for diagnosis of aPAP and for sites who wish to schedule a CT prior to screening.

TIME WINDOW:

To be done at a time-point allowing test result availability at Screening or Baseline (Visit 1 or 2). The procedure and timing will be described in a trial specific instruction.

ACTIVITIES AND ASSESSMENTS:

- Informed consent - Signed and dated by the subject and by the person who conducted the informed consent discussion will be collected prior to any trial related procedures described in this protocol (*Section 13.1.3*).
- Anti-GM-CSF, if applicable (*Section 10.1.9.1*)
- CT, if applicable (*Section 10.1.6*)

7.2.1.2 Screening (Visit 1)

ACTIVITIES AND ASSESSMENTS:

At Screening (Visit 1), the following activities and assessments will be performed:

- Informed consent (if not done during pre-screening visit period, *Section 7.2.1.1*) - Signed and dated by the subject and by the person who conducted the informed

consent discussion will be collected prior to any trial related procedures described in this protocol (*Section 13.1.3*)

- Eligibility criteria - Assessment of inclusion and exclusion criteria (*Section 8.2* and *Section 8.3*)
- Demographics and Baseline data (*Section 10.3.1*)
- Medical history (*Section 10.3.2*)
- Physical examination (*Section 10.4.3*)
- Vital signs (*Section 10.4.4*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Laboratory safety assessments (haematology and clinical chemistry) (*Section 10.4.6*)
- Serum pregnancy test and instruction in contraceptive measures (*Section 10.5*)
- DSS (*Section 10.1.8*)
- Arrangement for trial drug administration training (*Section 9.1.5*)

7.2.1.3 Baseline (Visit 2)

TIME WINDOW:

14 days (± 7 days) after Screening (Visit 1)

The CT scan can be done up to four weeks prior to Baseline (Visit 2)

ACTIVITIES AND ASSESSMENTS:

At Baseline (Visit 2), the following activities and assessments will be performed:

- Eligibility criteria check– Fulfilment of inclusion and exclusion criteria will be confirmed (*Section 8.2* and *Section 8.3*)
- Prior and Concomitant medication (*Section 10.3.3*)
- Urine and serum pregnancy test and evaluation of contraceptive measures (*Section 10.5*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- CT (*Section 10.1.6*).
- QoL score (*Section 10.1.7*)
- Electrocardiogram (ECG) (*Section 10.4.5*)
- Laboratory safety assessments (haematology and clinical chemistry) (*Section 10.4.6*)

- AEs (*Section 10.4.2*)
- Randomisation to trial treatment (*Section 9.2*)
- Samples for biomarkers, GM-CSF and anti-drug antibodies prior to administration of first dose of trial drug (*Section 10.1.9*)
- Dispense trial drug (*Section 9.1.4*)
- Administration of first dose of trial drug (*Section 9.1.5*)
- Sample for GM-CSF two hours after completion of administration of first dose of trial drug (*Section 10.1.9*)
- Subject Diary Card (*Section 10.4.2*)

7.2.1.4 Week 4 (Visit 3)

TIME WINDOW:

28 days (± 7 days) after Randomisation (Visit 2)

ACTIVITIES AND ASSESSMENTS:

At Week 4 (Visit 3), the following activities and assessments will be performed:

- Concomitant medication (*Section 10.3.3*)
- Physical examination (*Section 10.4.3*)
- Vital signs (*Section 10.4.4*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- QoL score (*Section 10.1.7*)
- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry) (*Section 10.4.6*)
- Biomarkers and GM-CSF prior to administration of trial drug in clinic (*Section 10.1.9*).
- Anti-drug antibodies prior to administration of trial drug in clinic (*Section 10.1.9*)
- AEs (*Section 10.4.2*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)
- Administration of trial drug at the site (*Section 9.1.5*)
- Dispense trial drug (*Section 9.1.4*)
- Sample for GM-CSF two hours after completion of administration of trial drug (*Section 10.1.9*)

7.2.1.5 Week 8 (Visit 4)

TIME WINDOW:

56 days (± 7 days) after Randomisation (Visit 2)

ACTIVITIES AND ASSESSMENTS:

At Week 8 (Visit 4), the following activities and assessments will be performed:

- Concomitant medication (*Section 10.3.3*)
- Lung function tests (*Section 10.1.2*)
- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*)
- AEs (*Section 10.4.2*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)
- Dispense trial drug (*Section 9.1.4*)

7.2.1.6 Week 12 (Visit 5)

TIME WINDOW:

84 days (± 7 days) after Randomisation (Visit 2)

ACTIVITIES AND ASSESSMENTS:

At Week 12 (Visit 5), the following activities and assessments will be performed:

- Concomitant medication (*Section 10.3.3*)
- Physical examination (*Section 10.4.3*)
- Vital signs (*Section 10.4.4*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- QoL score (*Section 10.1.7*)
- ECG (*Section 10.4.5*)
- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry) (*Section 10.4.6*)
- Biomarkers and anti-drug antibodies prior to administration of trial drug in clinic (*Section 10.1.9*)
- AEs (*Section 10.4.2*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)

- Administration of trial drug at the site (*Section 9.1.5*)
- Dispense trial drug (*Section 9.1.4*)

7.2.1.7 Week 16 (Visit 6)

TIME WINDOW:

112 days (± 7 days) after Randomisation (Visit 2)

ACTIVITIES AND ASSESSMENTS:

At Week 16 (Visit 6), the following activities and assessments will be performed:

- Concomitant medication (*Section 10.3.3*)
- Lung function tests (*Section 10.1.2*)
- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*)
- AEs (*Section 10.4.2*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)
- Dispense trial drug (*Section 9.1.4*)

7.2.1.8 Week 20 (Visit 7)

TIME WINDOW:

140 days (± 7 days) after Randomisation (Visit 2)

ACTIVITIES AND ASSESSMENTS:

At Week 20 (Visit 7), the following activities and assessments will be performed:

- Concomitant medication (*Section 10.3.3*)
- Lung function tests (*Section 10.1.2*)
- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*)
- AEs (*Section 10.4.2*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)
- Dispense trial drug (*Section 9.1.4*)

7.2.1.9 Week 24 (Visit 8)

TIME WINDOW:

168 days (± 7 days) after Randomisation (Visit 2)

The CT scan can be performed seven days prior to or after Week 24 (Visit 8)

ACTIVITIES AND ASSESSMENTS:

At Week 24 (Visit 8), the following activities and assessments will be performed:

- Concomitant medication (*Section 10.3.3*)
- Physical examination (*Section 10.4.3*)
- Vital signs (*Section 10.4.4*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- CT (*Section 10.1.6*)
- QoL score (*Section 10.1.7*)
- DSS (*Section 10.1.8*)
- ECG (*Section 10.4.5*)
- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*)
- Biomarkers and anti-drug antibodies prior to administration of trial drug in clinic (*Section 10.1.9*)
- AEs (*Section 10.4.2*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)
- Administration of trial drug at the site (*Section 9.1.5*)
- Dispense trial drug (*Section 9.1.4*)

7.2.1.10 4-Week Telephone Follow-up (Visit 9)

TIME WINDOW:

28 days (±3 days) after Week 24 (Visit 8).

ACTIVITIES AND ASSESSMENTS:

At 4-Week Telephone Follow-up (Visit 9), the following activities and assessments will be performed:

- AEs (*Section 10.4.2*)
- Medication/therapy for aPAP (*Section 10.3.3*)

7.2.1.11 12-Week Follow-up (Visit 10)

TIME WINDOW:

84 days (±14 days) after Week 24 (Visit 8)

ACTIVITIES AND ASSESSMENTS:

At 12-week Follow-up (Visit 10), the following activities and assessments will be performed:

- Medication/therapy for aPAP (*Section 10.3.3*)

- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- QoL score (*Section 10.1.7*)
- AEs (*Section 10.4.2*)
- Samples for anti-drug antibodies (*Section 10.1.9*)

For subjects using molgramostim in the Follow-up period:

- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*).
- Administration of trial drug at the site (*Section 9.1.5*)
- Subject Diary Card (*Section 10.4.2*)
- Dispense trial drug (*Section 9.1.4*)
- Treatment compliance (*Section 9.5*)

7.2.1.12 24-Week Follow-up (Visit 11)

TIME WINDOW:

168 days (±14 days) after Week 24 (Visit 8)

ACTIVITIES AND ASSESSMENTS:

At 24-week Follow-up (Visit 11), the following activities and assessments will be performed:

- Physical examination (*Section 10.4.3*)
- Vital signs (*Section 10.4.4*)
- Medication/therapy for aPAP (*Section 10.3.3*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- QoL score (*Section 10.1.7*)
- DSS (*Section 10.1.8*)
- ECG (*Section 10.4.5*)
- AEs (*Section 10.4.2*)
- Samples for anti-drug antibodies (*Section 10.1.9*)

For subjects using molgramostim in the Follow-up period:

- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*).
- Administration of trial drug at the site (*Section 9.1.5*).
- Subject Diary Card (*Section 10.4.2*).
- Dispense trial drug (*Section 9.1.4*).
- Treatment compliance (*Section 9.5*)

7.2.1.13 36-Week Follow-up (Visit 12)

Visit 12 is **not** applicable to subjects where the informed consent was obtained after amendment 11 was approved by the national authorities.

TIME WINDOW:

252 days (± 14 days) after Week 24 (Visit 8)

ACTIVITIES AND ASSESSMENTS:

At 36-week Follow-up (Visit 12), the following activities and assessments will be performed:

- Medication/therapy for aPAP (*Section 10.3.3*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- AEs (*Section 10.4.2*)

For subjects using molgramostim in the Follow-up period:

- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry) (*Section 10.4.6*)
- Subject Diary Card (*Section 10.4.2*)
- Dispense trial drug (*Section 9.1.4*)
- Treatment compliance (*Section 9.5*)

7.2.1.14 48-Week Follow-up (Visit 13)

Visit 13 is **not** applicable to subjects where the informed consent was obtained after amendment 11 was approved by the national authorities.

TIME WINDOW:

336 days (± 14 days) after Week 24 (Visit 8)

ACTIVITIES AND ASSESSMENTS:

At 48-week Follow-up (Visit 13), the following activities and assessments will be performed:

- Physical examination (*Section 10.4.3*)
- Vital signs (*Section 10.4.4*)

- Medication/therapy for aPAP (*Section 10.3.3*)
- (A-a)DO₂ and PaO₂ (*Section 10.1.1*)
- Lung function tests (*Section 10.1.2*)
- 6MWT (*Section 10.1.3*)
- Dyspnoea score (*Section 10.1.4*)
- Cough scores (*Section 10.1.5*)
- QoL score (*Section 10.1.7*)
- DSS (*Section 10.1.8*)
- ECG (*Section 10.4.5*)
- AEs (*Section 10.4.2*)

For subjects using molgramostim in the Follow-up period:

- Serum pregnancy test (*Section 10.5*)
- Laboratory safety assessments (haematology and clinical chemistry), (*Section 10.4.6*)
- Subject Diary Card (*Section 10.4.2*)
- Treatment compliance (*Section 9.5*)

7.2.2 Trial Flow Chart

Table 1 Trial Flow Chart

Visit number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	4-Week Telephone F-up	12-Week F-up	24-Week F-up	36-Week F-up ^P	48-Week F-up ^P
Day		14 days after Screening	28 days after Randomisation	56 days after Randomisation	84 days after Randomisation	112 days after Randomisation	140 days after Randomisation	168 days after Randomisation	28 days after Visit 8	84 days after Visit 8	168 days after Visit 8	252 days after Visit 8	336 days after Visit 8
Window		± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 3 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days
Informed consent ^a	X												
Eligibility criteria	X	X ^b											
Demographics	X												
Medical history	X												
Prior/Concomitant medication/therapy ^c		X	X	X	X	X	X	X					
Treatment for aPAP									X	X	X	X	X
Pregnancy test and contraceptive check	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d		X ^d	X ^d	X ^d	X ^d
Physical Exam	X		X		X			X			X		X
Vital signs	X		X		X			X			X		X
(A-a) DO ₂ , PaO ₂ ^e	X	X	X		X			X		X	X	X	X
Lung function tests ^f	X	X	X	X	X	X	X	X		X	X	X	X
6MWT ^g	X	X	X		X			X		X	X	X	X
Laboratory Safety Analyses ^h	X	X	X	X	X	X	X	X		X	X	X	X

Visit number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	4-Week Telephone F-up	12-Week F-up	24-Week F-up	36-Week F-up ^P	48-Week F-up ^P
Day		14 days after Screening	28 days after Randomisation	56 days after Randomisation	84 days after Randomisation	112 days after Randomisation	140 days after Randomisation	168 days after Randomisation	28 days after Visit 8	84 days after Visit 8	168 days after Visit 8	252 days after Visit 8	336 days after Visit 8
Window		± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	± 3 Days	± 14 Days	± 14 Days	± 14 Days	± 14 Days
ECG		X			X			X			X		X
GM-CSF ⁱ		X	X										
Anti-Drug antibodies	X ^a	X ^j	X ^j		X ^j			X ^j		X ^j	X ^j		
Biomarkers ^k		X	X		X			X					
CT		X ^l						X ^l					
DSS	X							X			X		X
Dyspnoea score ^m	X	X	X		X			X		X	X	X	X
Cough scores		X	X		X			X		X	X		X
QoL score		X	X		X			X		X	X		X
Trial drug administration training	X ⁿ												
Randomisation		X											
Trial drug dosing in the clinic		X	X		X			X		X	X		
AEs		X	X	X	X	X	X	X	X	X	X	X	X
Subject Diary Card ^o		X	X	X	X	X	X	X		X	X ^q	X	X
Dispense trial drug		X	X	X	X	X	X	X		X	X ^q	X	
Compliance			X	X	X	X	X	X		X	X	X	X

- ^a Only related to anti-GM-CSF. Anti-GM-CSF blood sampling to be done during pre-screening period at trial sites that do not perform anti-GM-CSF as routine for aPAP diagnosis. Only subjects without available data will have a sample taken before screening to confirm diagnosis. Anti-GM-CSF blood sampling should be done only after collection of informed consent at such trial sites. Informed consent also to be taken in sites who conduct CT before screening.
- ^b Re-check of eligibility criteria.
- ^c Prior medication/therapy is defined as medication/therapy administered prior to first dose of trial medication. All medication/therapy administered after first dose of trial medication is considered concomitant medication/therapy.
- ^d Serum pregnancy test at Screening (Visit 1), at dosing at Baseline (Visit 2) and at all subsequent visits during trial. A urine pregnancy test will also be performed at dosing at Baseline (Visit 2) in order to immediately confirm that the subject is not pregnant and meets the inclusion criterion. Pregnancy tests (urine or serum) must continue at monthly intervals during treatment with inhaled molgramostim. Pregnancy tests at visit 10, 11, 12 and 13 for subjects who are not treated with inhaled molgramostim during the follow-up period are not mandatory.
- ^e Capillary sampling for blood gas analysis may be used instead of an arterial blood gas sample at Screening Visit 1, Visit 3, Visit 5 and all Follow-up Visits at sites that routinely use this method. Arterial sampling for blood gas is mandatory at Baseline (Visit 2) and Visit 8.
- ^f VC, DLCO, FEV₁, and FVC (all % predicted).
- ^g The need for supplemental O₂ during the procedure will be determined as part of the test at Screening or Baseline. The same O₂ flow will be used at the subsequent tests in the trial.
- ^h Haematology and clinical chemistry.
- ⁱ Samples for GM-CSF to be collected prior to 1st dose of trial drug and two hours after completion of administration of 1st dose of trial drug at Baseline (Visit 2) and prior to dosing and two hours after dosing at Week 4 (Visit 3).
- ^j Samples for anti-drug antibodies to be collected prior to administration of trial drug.
- ^k Biomarkers to be analysed: KL-6, CEA, Cyfra 21-1, SP-A, SP-B, SP-C, SP-D, and LDH.
- ^l CT can be done 4 weeks prior to the baseline visit (informed consent needs to be collected if before screening visit) and 7 days before or after Visit 8.
- ^m Dyspnoea score (BDS) to be performed before the 6MWT and also immediately after the 6MWT.
- ⁿ The subject must be trained in the inhalation and medical device maintenance procedure prior to administration of first dose of trial drug. The time and place for this training will be agreed upon at the screening visit.
- ^o Diary card to collect safety information to be given to the subject and collected at the next visit. The subject will be asked to record any AEs and answer questions regarding lung toxicity and known systemic effects in the diary card.
- ^p Visit 12 and visit 13 is only applicable to subjects who have signed the informed consent before amendment 11 to the protocol was approved by the local authorities.
- ^q Only applicable for subjects who have signed the informed consent before amendment 11 to the protocol was approved by the local authorities

7.3 Trial Period

Expected timelines:

The duration of trial participation for each subject is approximately 50 to 78 weeks:

- Screening period for the subjects is 14 days (+/- 7 days)
- Double-blind period up to 24 weeks (+/- 7 days)
- Open-label period for 24 or 48 weeks (+/- 14 days)

7.4 End of Trial

The last visit is either the 24-Week Follow-up (visit 11) or 48-Week Follow-up (Visit 13).

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

8 SELECTION OF TRIAL POPULATION

8.1 Number of Subjects

A total of 90 subjects are intended to be randomised. See *Section 12.2* for calculation of sample size.

8.2 Inclusion Criteria

The patients must meet all of the following criteria to be eligible to enter the trial:

- aPAP diagnosed by CT, or by biopsy, or by Broncho Alveolar Lavage (BAL), and by increased GM-CSF autoantibodies in serum
- Stable or progressive aPAP (i.e. absolute VC not improved by more than 5% and/or DLCO not improved by more than 10% - assessed from medical records) during a minimum period of two months prior to the Baseline visit
- PaO₂ <75 mmHg/<10 kPa at rest, OR desaturation of >4 percentage points on the 6MWT
- An (A-a)DO₂ of minimum 25 mmHg/3.33 kPa
- Female or male ≥18 years of age
- Females who have been post-menopausal for >1 year or females of childbearing potential after a confirmed menstrual period using a highly efficient method of contraception (i.e. a method with <1% failure rate such as combined hormonal contraception, progesterone-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, sexual abstinence), during and until 30 days after last dose of trial treatment. Females of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at dosing at Baseline (Visit 2) and must not be lactating
- Males agreeing to use condoms during and until 30 days after last dose of trial treatment, or males having a female partner who is using adequate contraception as described above
- Willing and able to provide signed informed consent
- 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

8.3 Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the trial:

- Diagnosis of hereditary or secondary PAP
- WLL within one month of Baseline
- Treatment with GM-CSF within three months of Baseline
- Treatment with rituximab within six months of Baseline
- Treatment with plasmapheresis within three months of Baseline

- Treatment with any investigational medicinal product within four weeks of Screening
- Concomitant use of sputum modifying drugs such as carbocystein or ambroxol
- History of allergic reactions to GM-CSF
- Connective tissue disease, inflammatory bowel disease or other autoimmune disorder requiring treatment associated with significant immunosuppression, e.g. more than 10 mg/day systemic prednisolone
- Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product
- History of, or present, myeloproliferative disease or leukaemia
- Known active infection (viral, bacterial, fungal or mycobacterial)
- Apparent pre-existing concurrent pulmonary fibrosis
- Any other serious medical condition which in the opinion of the investigator would make the patient unsuitable for the trial

8.4 Withdrawal of Subjects from Therapy or Assessment

8.4.1 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)
- Subject is lost to Follow-up
- Other reason(s)

The reason and date the subject is withdrawn from the trial will be documented in the electronic case report form (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 24 if withdrawn during the Double-blind treatment period).

All AEs should be followed-up according to *Section 11.2*.

If a subject is withdrawn from the trial, all data collected until the time of withdrawal will be used in the analyses.

Subjects who withdraw before randomisation will be considered screen failures.

8.4.2 Discontinuation of Double-Blind Treatment

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

Potential reasons for discontinuation of double-blind treatment are:

- Lack of efficacy/worsening of disease
- Unacceptable AE

- Serious hypersensitivity reaction
- Pregnancy

Those who discontinue double-blind treatment will not automatically be withdrawn from the trial but will be encouraged to continue to follow the same visit schedule.

For example: if double-blind treatment is discontinued at Week 8 (Visit 4) the subject will be encouraged to attend the remaining visits in the Double-blind treatment period (Weeks 12, 16, 20 and 24) and continue into the Follow-up period. If the subject is reluctant to agree to 4-weekly visits, the investigator should request attendance at Week 24 (Visit 8) as a minimum.

The reason and date the subject is discontinued from double-blind treatment will be documented in the eCRF.

Subjects who fulfil the criteria for rescue treatment will be scheduled for a WLL as described in *Section 9.4*. Subjects receiving a WLL should continue Double-blind treatment and attend the remaining visits in the Double-blind treatment period and then continue into the Follow-up period.

8.5 Premature Termination of the Trial

The investigator or the sponsor may terminate this trial prematurely for any reasonable cause. The Independent Ethics Committees (IECs) 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 enrolled in the trial, or potential trial subjects

A decision on the part of the sponsor to suspend or discontinue development of the IMP

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

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

9 TREATMENT OF SUBJECTS

9.1 Investigational Medicinal Products

9.1.1 Treatment Regimens

Subjects will be randomised to receive double-blind treatment for up to 24 weeks with either:

- inhaled molgramostim (300 µg) administered once daily,
- inhaled molgramostim (300 µg) and matching placebo administered intermittently (12 cycles of seven days molgramostim followed by seven days placebo; both administered once daily) or
- inhaled placebo administered once daily.

In the Follow-up period all subjects will receive treatment with inhaled molgramostim (300 µg) administered intermittently (12 or 24 cycles of seven days molgramostim followed by seven days off-treatment) for 24 or 48 weeks. For subjects who entered the Follow-up period before Amendment 11 was approved by the national authorities, treatment with molgramostim in the Follow-up period is not mandatory.

Treatment with molgramostim in the Follow-up period should be discontinued in case of disease worsening and/or safety concerns.

9.1.2 Identity of Investigational Medicinal Products

Each vial of molgramostim contains 250 µg/mL molgramostim in 1.2 mL solution. Matching placebo will contain the same constituents but without the active molgramostim.

9.1.3 Manufacturing, Packaging and Labelling of Investigational Medicinal Product

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

Individual medication kits containing double-blind trial medication for one week will be supplied in adequate amounts at the dispensing visits. Every kit will be labelled with a unique medication number, which also appear on a tear-off part of the label.

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

9.1.4 Storage and Handling of Investigational Medicinal Product

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 and 20 (Visits 3, 4, 5, 6, and 7) during the Double-blind treatment period.

Unblinded IMP kits will be dispensed to the subject at Week 24 post-randomisation and at Follow-Up Weeks 12, 24 and 36 (Visits 8, 10, 11 and 12).

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

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

9.1.5 Investigational Medicinal Product Administration and Training

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

All subjects, investigators and trial nurses will be trained in IMP administration and medical device maintenance procedure. The training of the subjects will be arranged prior to administration of the subject's first dose of IMP and checked in clinic on first dosing. The subject will also receive written instructions.

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

9.2 Method of Assigning Subjects to Treatment Groups

At Screening (Visit 1), the subject will be assigned a site-specific subject number that will continue to be the unique identifier throughout the trial. The subject number will be generated automatically by the electronic data capture system used in the trial. The subject number will be in the following format XX-YYY. The letter XX is the site number and YYY the consecutive subject number starting at 001 at each site.

At the Baseline visit, eligible subjects will be centrally assigned to one of the three Double-blind treatment groups through an interactive web response system (IWRS). Randomisation will be stratified according to whether or not a WLL has been conducted within 2 months prior to the Baseline visit. The system will assign unique medication kits number to each subject at each dispensing visit.

Medication kits to be used in the Follow-up period are not blinded.

9.2.1 Randomisation

A randomisation list will be prepared by TFS's statistical department, who will store the list in a secure folder until unblinding has taken place.

9.2.2 Subject Identification List

The investigator will maintain a list of all subjects enrolled 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.

9.3 Blinding

All subjects will inhale IMP once daily during the Double-blind treatment period. Blinding will be ensured by the use of a matching placebo.

The packaging and labelling of the investigational products for the Double-blind treatment period will contain no evidence of their identity and it is not considered possible to differentiate between the investigational products solely by sensory evaluation.

9.3.1 Breaking the Randomisation Code

Unblinding of a single subject may occur for emergency purposes only. Investigators should note that the occurrence of a Serious Adverse Event (SAE) should not routinely precipitate the immediate unblinding of the label. If the treating physician considers it necessary to unblind the study medication for medical reasons, unblinding can be done using IWRS – and if possible, after prior contact with the Sponsor. The date and the event making it necessary to unblind the treatment randomization have to be documented in the patient files and in the case report form (CRF). The Sponsor will immediately be notified in case of emergency unblinding by an investigational site. In the case of a potential suspected unexpected serious adverse reaction (SUSAR) for an individual subject, Premier Research may break the blind. All investigational sites and the Sponsor's Pharmacovigilance Representative (Premier Research) have access to unblinding in the IWRS.

A Data Safety Monitoring Board (DSMB) will review unblinded safety data as part of the safety surveillance of the trial. A statistician from TFS who is independent from the trial will make the unblinded safety and tolerability data listings available to the DSMB according to TFS SOPs and the Statistical Analysis Plan. All study team members will remain blinded.

Unblinding of the clinical trial will take place when a final validated database for the 24-week double-blind period has been produced, the statistical analysis specified in this protocol has been reviewed in relation to the blinded data actually obtained and the Statistical Analysis Plan (SAP) has been approved.

9.4 Prior and Concomitant Therapy

The use of concomitant medicines or other treatment regimen during the 24-week Double-blind treatment period should be kept at a minimum and should be kept as stable as possible. Medication/treatment, which is considered necessary for subject safety and well-being, may be given at the discretion of the investigator. Examples of such medications/treatments are:

- WLL (rescue therapy) - The criteria for performing WLL is clinical worsening of aPAP based on symptoms, reduced exercise capacity and/or findings of hypoxemia or desaturation according to the Investigator's judgement. The reason(s) for conducting WLL will be documented.
- Oxygen supplementation

Sputum modifying medications such as carbocystein and ambroxol are prohibited for participating subjects in the Double-blind period of this trial. Medications detailed in the exclusion criteria which are rituximab and therapy associated with significant immunosuppression are also not allowed (e.g. more than 10mg/day systemic prednisolone) while the subject is treated with IMP in the Double-blind or Follow-up periods. Other rhGM-CSF products are not allowed during the Double-blind or Follow-up periods.

For subjects who discontinue the double-blind trial treatment and for all subjects in the Follow-up period, use of medications to specifically treat aPAP will be recorded in the eCRF. Information will be collected regarding:

- concomitant medications, treatments and procedures used to treat aPAP
- medication or treatments which may alter the course of aPAP
- medication or treatments used to treat AEs

No other information on concomitant medications, treatments or procedures in the Follow-up period will be collected.

The use of concomitant medication by the subject must be recorded in the appropriate sections of the eCRF (*Section 10.3.3*).

9.5 Treatment Compliance

Subject compliance in the Double-blind treatment and Follow-up periods 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. To verify correct treatment in the Double-blind period the subjects will apply the tear-off label from the weekly kit in the Diary Card (see Section 10.4.2).

9.6 Drug Accountability

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

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

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.

9.7 Post-Trial Treatment

After completion of the trial, subjects who require further treatment will be offered treatment with molgramostim in in a Compassionate Use Programme, where national regulations so allow.

10 TRIAL ASSESSMENTS

10.1 Efficacy Assessments

10.1.1 Blood Gas Analysis

The following variables will be assessed from an arterial blood gas sample at the timepoints shown in *Table 1*:

- (A-a)DO₂ (mmHg/kPa)
- PaO₂ (mmHg/kPa)
- PaCO₂ (mmHg/kPa)

Sites that are experienced in the use of capillary sampling for blood gas analysis as part of their standard care, may use this option instead of an arterial blood gas sample at Screening (Visit 1), Weeks 4 and 12 (Visits 3 and 5) and all Follow-up Visits, but an arterial sample for blood gas is mandatory at Baseline (Visit 2) and Week 24 (Visit 8).

Subjects should rest for at least 10 minutes before puncture and the sample should be taken in supine position. Trial specific instructions will be provided in a separate document. The sample will be analysed in accordance with local routines.

If possible, arterial blood gases at Baseline should be conducted with the subject breathing room air. If the subject cannot tolerate temporary discontinuation of supplemental oxygen during blood gas sampling at Baseline, blood gas sampling at subsequent visits should be conducted using the same oxygen flow rate as was used at Baseline.

The (A-a)DO₂ will be calculated based on PaO₂, PaCO₂ and the ambient atmospheric pressure based on a standard equation (see section 10.2.1).

10.1.2 Lung Function Tests

The following lung function variables will be assessed at the timepoints shown in *Table 1*:

- VC (% predicted)
- DLCO (% predicted)
- FEV₁ (% predicted)
- FVC (% predicted)

VC, DLCO, FEV₁ and FVC will be assessed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force: Standardisation of lung function testing [36] by laboratory personnel with documented training in lung function testing. DLCO will be adjusted for haemoglobin value. VC, FEV₁ and FVC during the Double-blind period will be assessed using equipment provided by the Sponsor and centrally read. The VC (% predicted), FEV₁ (% predicted) and FVC (% predicted) for the DB period will be calculated based on a known standard.

VC, FEV₁ and FVC in the Follow-up period and DLCO will be assessed using local, appropriately calibrated equipment.

Trial specific instructions will be provided in a separate document.

10.1.3 Tolerance to Exercise

Tolerance to exercise will be assessed at the timepoints shown in *Table 1*:

- The 6MWT (Pre and Post walk dyspnoea score using the BDS, Blood oxygen saturation (SpO₂) (%) at start, Worst SpO₂ (%) during the walk, Distance walked (m), Duration of the walk (minutes and seconds), O₂ flow rate, reason for stopping early if applicable)

The 6MWT will be performed in accordance with ATS/ERS Task Force: Standardisation of lung function testing [36] by technicians with documented training and experience of performing the 6MWT in accordance with the referred ATS/ERS guidance. Trial specific instructions will be provided in a separate document.

If possible, the 6MWT should be conducted using room air. If the subject requires O₂ supplementation at rest, an O₂ titration procedure will be followed as part of the 6MWT at Screening in order to determine the amount of oxygen supplementation required for the subject to complete the test. The same flow of oxygen should then be used at the subject's subsequent tests in the trial, if possible.

10.1.4 Dyspnoea Score

The Dyspnoea score will be assessed at the timepoints shown in *Table 1*.

Dyspnoea severity will be established using the Borg CR10 Scale (BDS - *Appendix C*). The BDS will be used before the 6MWT and immediately after the 6MWT. Questionnaires in the local language will be used.

10.1.5 Cough Scores

Subjects will be asked to score the severity and frequency of coughs on a visual analogue scale (Cough Questions - CQ - *Appendix D*) at the timepoints shown in *Table 1*. Questions will be in the local language.

10.1.6 CT Scoring

High Resolution CT scans will be performed at the timepoints shown in *Table 1* according to a trial-specific image acquisition protocol.

A trial specific instruction describing the handling, transferring, blinding, distribution, assessment, result processing, and filing of data will be provided to all concerned personnel.

Two independent and blinded assessors will examine the scans. The assessments will be performed centrally on a per subject basis; the Baseline (Visit 2) and Week 24 (Visit 8) scans will be assessed at the same time for the individual subjects. The extent of ground-glass opacification in the CT scans will be quantified visually, as previously described [18].

The improvement will be graded as: Improved / Worsened / No change / Data missing – Impossible to evaluate.

The CT scans will also be evaluated for safety and any detrimental effects of treatment detected at Week 24 (Visit 8) will be recorded as AEs.

Further the CT scans will be evaluated using quantitative assessment at a sufficiently qualified laboratory.

10.1.7 Quality of Life Score

Subjects will be asked to assess their QoL at the timepoints shown in *Table 1*.

Subjects will be asked to complete the following questionnaires:

- The St Georges Respiratory Questionnaire (SGRQ) is a respiratory specific questionnaire which is available in the local language. The symptoms component with 3-month symptoms recall will be used, *Appendix A*. This disease-specific instrument

has been designed to measure impact on QoL in subjects with obstructive airway disease. This assessment is considered relevant for use in subject population of this trial.

- The EuroQol-5D (EQ-5D) is a more general questionnaire which is widely used to measure health outcome in terms of mobility, self care, usual activities, pain/discomfort, anxiety/depression. The 5 level instrument (EQ-5D-5L) which uses a 5-point scale (no problems, slight problems, moderate problems, severe problems, and extreme problems) will be used in the local language, *Appendix B*. This instrument will be used to measure overall self-rated health status.

10.1.8 Disease Severity Score

The DSS will be assessed at the timepoints shown in *Table 1*.

The DSS is based on the presence of symptoms and degree of reduction in PaO₂ determined with the individual breathing room air in the supine position [37].

The DSS is a 5-point score as follows:

- 1 = no symptoms and PaO₂ ≥ 70 mmHg
- 2 = symptomatic and PaO₂ ≥ 70 mmHg
- 3 = 60 mmHg ≤ PaO₂ < 70 mmHg
- 4 = 50 mmHg ≤ PaO₂ < 60 mmHg
- 5 = PaO₂ < 50 mmHg.

If possible, the blood gas assessment should be conducted with the subject breathing room air (see 10.1.1). For subjects requiring supplemental oxygen during the blood gas assessment the DSS will be based on the PaO₂ obtained while breathing oxygen.

10.1.9 Biomarkers in Serum

10.1.9.1 GM-CSF and Anti-Drug Antibodies

Blood samples will be taken at the timepoints shown in *Table 1*.

At Baseline (Visit 2) and at Week 4 (Visit 3), samples for GM-CSF will be collected prior to dosing of trial drug. An additional sample for analysis of GM-CSF will be collected two hours after completion of trial drug administration at Baseline (Visit 2) and at Week 4 (Visit 3).

All samples for anti-drug antibodies will be collected prior to dosing at the appropriate clinic visit.

Analyses for GM-CSF and anti-drug antibodies (anti-GM-CSF, anti-Polyethylene glycol (anti-PEG) and anti-recombinant Human Albumin (anti-rHA)) antibodies will be performed using a GLP validated method.

10.1.9.2 Other Biomarkers

Blood samples will be taken at the timepoints shown in *Table 1*. The following biomarkers will be analysed: Krebs von den Lungen-6 (KL-6), Carcinoembryonic antigen (CEA), Surfactant Protein A (SP-A), Surfactant Protein B (SP-B), Surfactant Protein C (SP-C), Surfactant Protein D (SP-D), Cytokeratin Fragment 19 (Cyfra 21-1) and Lactate Dehydrogenase (LDH) after 4, 12, and 24-weeks treatment.

Analysis for these biomarkers will be performed by a central laboratory using validated methods. LDH will be analysed from the standard clinical chemistry sample.

10.2 Primary, Secondary, and Exploratory Endpoints

10.2.1 Primary Endpoint:

- Absolute change from baseline of (A-a)DO₂ after 24-weeks treatment.

At each visit, (A-a)DO₂ will be calculated centrally using the equation:

$$Aa \text{ Gradient} = \left(F_i O_2 (P_{atm} - P_{H_2O}) - \frac{P_a CO_2}{0.8} \right) - P_a O_2$$

where F_iO₂ is fraction of inspired oxygen

P_{atm} is ambient atmospheric pressure

P_{H₂O} is saturated vapour pressure of water at body temperature (set to 47 mmHg / 6.266 kPa)

P_aCO₂ is arterial partial pressure of carbon dioxide

P_aO₂ is arterial partial pressure of oxygen

10.2.2 Secondary Endpoints:

10.2.2.1 Key Secondary Endpoints

- Change from baseline in 6MWD after 24-weeks treatment
- Change from baseline in SGRQ total score after 24-weeks treatment
- Time to WLL during 24-weeks treatment
- Number of AEs, SAEs, ADRs, severe AEs and AEs leading to treatment discontinuation, including clinically significant changes in laboratory tests and electrocardiographic (ECG) variables, during 24-weeks treatment

10.2.2.2 Further Secondary Endpoints:

- Absolute change from baseline in VC (% predicted), DLCO (% predicted), FEV₁ (% predicted) and FVC (% predicted), and relative change from baseline in PaO₂ after 24-weeks treatment
- Number of subjects with >5 mmHg/>0.67 kPa and number of subjects with >10 mmHg/>1.33 kPa improvement in (A-a)DO₂ after 24-weeks treatment
- Number of subjects with >5 percentage points and number of subjects with >10 percentage points improvement in VC (% predicted) after 24-weeks treatment
- Number of subjects with >10 percentage points improvement in DLCO (% predicted) after 24-weeks treatment
- Number of subjects with >10 percentage points improvement in FEV₁ (% predicted), FVC (% predicted) after 24-weeks treatment
- Number of subjects with >10% relative improvement in PaO₂ after 24-weeks treatment
- Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 24-weeks treatment
- Change from baseline in dyspnoea score and cough scores after 24-weeks treatment

- Number of subjects with improved CT score after 24-weeks treatment

10.2.3 Exploratory Endpoints

10.2.3.1 Double-Blind Treatment Period

- Absolute change from baseline of (A-a)DO₂, VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), FVC (% predicted), and relative change from baseline of PaO₂ after 4 and 12-weeks, treatment
- Time period during which the (A-a)DO₂ level is maintained below Baseline –10mmHg
- Number of subjects with improved tolerance to exercise (increase in distance walked ≥ 50 m or desaturation <4 percentage points on the 6MWT) after 4 and 12-weeks treatment
- Time period during which the improvement in tolerance to exercise is maintained
- Change from baseline in dyspnoea score and cough scores after 4 and 12-weeks treatment
- Number of subjects with improved QoL (change of ≥4 units on the SGRQ/number of subjects with 'no problems' in the EQ-5D-5L), after 4, 12, and 24-weeks treatment
- Change in serum concentration of biomarkers; KL-6, CEA, SP-A, SP-B, SP-C, SP-D, Cyfra 21-1 and LDH after 4, 12, and 24-weeks treatment
- Levels of anti-GM-CSF after 4, 12 and 24-weeks treatment
- Change in serum concentration of GM-CSF post first dose of trial drug and after 4-weeks treatment
- Number of subjects in need for oxygen supplement therapy during 24-weeks treatment
- The distribution of DSS at Screening and at Week 24
- The percentage of subjects with DSS 1 or 2 at Week 24

10.2.3.2 Follow-up period

- Number of subjects requiring WLL, or other treatment for aPAP and number of treatment courses required during 24-weeks or 48-weeks follow-up
- Time to WLL, or other treatment for aPAP during 24-weeks or 48-weeks follow-up
- Absolute change from baseline in (A-a)DO₂ and VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), and FVC (% predicted), and relative change from baseline of PaO₂ after 12, 24, 36 and 48-weeks follow-up
- Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 12, 24, 36 and 48-weeks follow-up
- Number of AEs, severe AEs, SAEs and ADRs, including clinically significant changes in laboratory tests and ECG variables, during 24-weeks or 48-weeks follow-up
- Levels of anti-GM-CSF after 12 and 24 weeks follow-up
- The distribution of DSS after 24 and 48-weeks follow-up
- The percentage of subjects with DSS 1 or 2 after 24 and 48-weeks follow-up

10.3 Demographic and Other Baseline Characteristics

10.3.1 Demographic and Baseline Data

The following demographic and baseline data will be collected at Screening (Visit 1):

- Date of birth
- Weight and height
- Sex
- Race (White/Asian/Black/American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander, according to FDA)
- Date of aPAP diagnosis
- Smoking (Previous/Current/Never)
- Previous exposure to GM-CSF (Yes/No) (Administration within three months of Baseline is an Exclusion criterion, *Section 8.3*)
- Previous WLLs (Total number, date for last WLL) (WLL within one month of Baseline is an Exclusion criterion, *Section 8.3*)

10.3.2 Medical History

Medical history will be recorded at Screening (Visit 1).

10.3.3 Recording of Prior and Concomitant Medication/Therapy

Prior and concomitant therapies allowed during the trial are detailed in *Section 9.4*.

Prior medication/therapy is defined as medication/therapy administered prior to first dose of trial medication. All medication/therapy administered after first dose of trial medication is considered concomitant medication/therapy.

At Baseline (Visit 2) prior medications/therapies administered within three months will be recorded. In the Double-blind treatment period at Weeks 4, 8, 12, 16, 20 and 24 (Visits 3, 4, 5, 6, 7 and 8) concomitant medication/therapy administered from first dose of Double-blind treatment given will be recorded.

In the Follow-up period at 4, 12, 24 and 48 weeks after the end of the Double-blind treatment period (4-week FU, 12-week FU, 24-week FU and 48-week FU Visits) only concomitant medications and treatments outlined in *Section 9.4* will be recorded.

The following information will be collected and recorded on the concomitant medication/therapy page of the eCRF throughout the trial for prior and concomitant medications: Drug name (product name), route, dose and units, frequency, indication, reference to AE if applicable, start date, end date or ongoing at the end of the trial will be recorded. Prior and concomitant medications will be coded using World Health Organisation (WHO) Drug Dictionary.

10.3.3.1 Whole Lung Lavage

WLL is applied as rescue therapy during the trial. The criterion for performing WLL is clinical worsening of aPAP based on symptoms, reduced exercise capacity and/or findings of hypoxemia or desaturation according to the Investigator's judgement. The reason(s) for conducting WLL should be documented. The date, when this criterion applies and thus an indication for WLL is present, will be recorded in the CRF.

The following information will be collected and recorded on the concomitant medication/therapy page of the eCRF throughout the trial for prior and concomitant WLL procedures: Date, start and end time, type of WLL, saline volume. Anesthesia drugs should be recorded as concomitant medication(s).

10.3.3.2 Oxygen Supplementation

Oxygen supplementation will be collected and recorded on the concomitant medication/therapy page of the eCRF throughout the trial for prior and concomitant supplementation.

Oxygen supplementation given only during assessments (according to *Section 10.1.1 or 10.1.3*) will not be recorded on the concomitant medication/therapy page, but under lung function and 6MWT pages, respectively.

10.4 Safety Assessments

10.4.1 Safety Variables

The following safety variables will be assessed:

- AEs
- Physical examination
- Vital signs
- Laboratory safety assessments
- HR-CT

10.4.2 Adverse Events

Any AEs will be reported during the trial period from Baseline (Visit 2) to the completion of the 24- week or 48-week Follow-up visits (Visit 11 and 13). The subjects will be encouraged to contact the clinic in between visits if they experience AEs or have any concerns. For further information of definitions and reporting of AEs and SAEs, see *Section 11*.

A Diary Card will be given to the subject at start of treatment at the Baseline Visit (Visit 2) and at Weeks 4, 8, 12, 16 and 20 (Visits 3, 4, 5, 6 and 7) at Weeks 12, 24 and 36 of the Follow-up period (Visits 10,11 and 12). In the Diary Card the subject will record any AEs and answer specific questions regarding potential pulmonary and systemic effects. The completed Diary Card will be collected at the next clinic visit (Visits 3, 4, 5, 6, 7, 8, 10, 11, 12 and 13). At these visits, the investigator will evaluate the safety information on the Diary Card and record any AEs on the eCRF.

10.4.3 Physical Examination

All subjects will undergo a standard physical examination at the timepoints shown in *Table 1*. Any abnormalities will be recorded in the eCRF.

10.4.4 Vital Signs

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

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

- Oral body temperature (°C)

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

10.4.5 Electrocardiogram

A 12-lead ECG will be assessed using a standard ECG machine according to local procedures at the time points shown in *Table 1*. Heart rate, QRS, PR and QT intervals will be recorded from the ECGs. The ECGs will be interpreted and signed and dated by the investigator or his/her designee. Results will be classified as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. All clinically significant abnormalities will be recorded as AEs.

10.4.6 Laboratory Safety Assessments

The laboratory safety analyses (haematology and clinical chemistry) will be performed by a central laboratory at the timepoints shown in *Table 1*. Sampling methods and procedures will be in accordance with local routine care.

The following laboratory safety parameters will be analysed:

Table 2 Laboratory Safety Parameters

Category	Laboratory Parameter
Haematology	Haemoglobin, Red Blood Cell Count (RBC), Red Blood Cell Distribution Width (RDW), Haematocrit (PCV/EVF), Mean cell volume (MCV), Mean cell haemoglobin (MCH), Mean cell haemoglobin concentration (MCHC), Platelet count, White cell count, and white cell differential absolute and percentage count: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Prothrombin Time International Normalised Ratio (PT-INR)
Clinical Chemistry	Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyl Transpeptidase (GGT), Alkaline Phosphatase, Bilirubin,, Urea, S-Creatinine, Potassium, Sodium, Calcium, Chloride, Phosphate, Total protein, Albumin, LDH*, C-Reactive Protein (CRP), and Glucose (non-fasting)

* LDH will be analysed as a biomarker

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

10.5 Pregnancy Test

A serum pregnancy test will be performed for female subjects at Screening (Visit 1), at dosing at Baseline (Visit 2) and at all subsequent visits during the Double-blind and Follow-up treatment period. 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.

10.6 Appropriateness of Measurements

Standardised methods for measurements of efficacy and safety variables will be used.

10.7 Handling of Laboratory Samples and Total Blood Volume

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.

Blood samples for efficacy and safety assessments will be taken at all visits, except for Visit 9, which is a telephone follow-up. For the Double-blind period of 24 weeks the amount of blood required per patient per visit varies between 10 mL and 53 mL pr. visit. The total amount needed for the Double-blind period is approximately 250 mL. For the Follow-up period of 24 or 48 weeks the total amount of blood required per patient is approximately 85 mL, with a maximum of 26.2 mL for one visit.

11 SAFETY

11.1 Definitions

11.1.1 Adverse Event

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.

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

11.1.2 Adverse Drug Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment: All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression reasonable causal relationship means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out.

11.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorised IMP or summary of product characteristics for an authorised product).

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

11.1.4 Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

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

Comments: 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 hospitalisation did in fact take place as a result of it. As a rule, hospitalisation is the admission to a hospital with at least one overnight stay.

The presentation of a patient in the emergency room (casualty center, health care center) alone without subsequent in-patient admission does not yet fulfill the criterion hospitalisation. 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).

11.2 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.

11.3 Reporting of Adverse Events

All trial subjects will be carefully monitored for the occurrence of AEs during the trial period from Screening (Visit 1) to the completion of the 48-week Follow-up visit (Visit 13). The investigator will collect AEs with 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

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.

11.4 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 Day 30 after the last visit. Reporting of SAEs will also be described in a trial-specific procedure.

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

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

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

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

THE INVESTIGATOR MUST CONTACT PREMIER RESEARCH BY EMAIL OR FAX DIRECTLY TO PREMIER RESEARCH PHARMACOVIGILANCE AND DEVICE SAFETY IN CASE OF ALL SERIOUS ADVERSE EVENTS (SAES) **WITHIN 24 HOURS AFTER AWARENESS** OF THE EVENT.

SAE REPORTING CONTACT DETAILS

Company: Premier Research

Department: Pharmacovigilance and Device Safety (PVDS)

E-mail: SavaraSafety@premier-research.com

Fax: +421 2 68203713

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

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

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

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

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

11.5 SUSAR Reporting Procedure

According to national legislation and European directives and guidelines, the sponsor of the clinical trial will report all SUSARs to the competent authority and Ethics Committee in all Member States concerned, to the European clinical trials database (Eudravigilance Clinical Trial Module - EVTCM), and if applicable, to FDA using a written Investigational New Drug Application (IND) safety report.

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

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

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

11.6 Adverse Events of Special Interest

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

11.7 Precautions/Overdose

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

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

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

Haematologic findings such as leucocytosis and neutrophilia may occur if overdose results in high systemic exposure. With high systemic doses of similar products the following symptoms have been observed: tachycardia, hypotension, dyspnoea, and flu-like symptoms. These symptoms abated quickly on symptomatic treatment. More information is available in the IB.

11.8 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 11.4*. 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.

11.9 Data Safety Monitoring Board

A DSMB comprised of independent pulmonologists from lung centers who are experts in interstitial lung disease, and in conducting clinical studies will be appointed and assigned for safety surveillance of the trial. The DSMB members will not be investigators in the study. All members of the DSMB will be unblinded to the treatment received by the subject and the subject identification. Unblinded data for DSMB review will be provided by a statistician from TFS who is independent of the study (see *Section 9.3.1*).

Details of the composition, roles and responsibilities and operating procedures of the DSMB will be described in a DSMB Charter. The DSMB will perform safety monitoring of the trial by reviewing pertinent safety data and will following the review make recommendations to the Sponsor and the coordinating PI whether changes in the study conduct are needed based on safety data, including adding additional safety measures. After each review round, the DSMB may recommend continuing, modifying or completely stopping the trial. An interim analysis will not be part of the DSMB process and the trial will continue during the data review rounds.

11.10 Safety Management Plan

The process of SAE-Assessment is performed by Premier Research. In this context a study specific "Safety Management Plan" has to be prepared before first subject is recruited into the study. The Safety Management Plan contains a detailed description of all procedures

concerning the documentation and reporting of AEs, SAEs and SUSARs. Additionally, the Safety Management Plan describes the preparation of the Development Safety Update Report (DSUR), the Benefit-Risk-Assessment and the process of immediate actions to prevent the trial patients from immediate risks.

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 Statistical and Analytical Plans

The trial will be unblinded and the primary analysis will be conducted after all subjects have completed the 24-week Double-blind period.

A separate SAP, which will provide the technical details of the statistical analysis outlined below, will be prepared for use in conjunction with this protocol.

Before the trial is unblinded, a blind review of the data will be completed. At that time, adjustments to the planned analyses may be identified based on, for example, the extent and timing of missing data. Confirmation of eligibility for analysis populations (see *Section 12.1.1*) will be confirmed at this time.

The data from the open-label Follow-up period will be presented descriptively.

The following details are related to the randomised, double-blind portion of the trial.

12.1.1 Data Sets to be Analysed

The subject population sets are defined as follows:

Full analysis set (FAS): All randomised subjects.

Per-protocol set (PPS): All randomised subjects who have completed Visit 8 and are deemed to have no important protocol deviations that could interfere with the objectives of this trial. This is a sub-population of the FAS.

Note: Important deviations of eligibility criteria and other deviations from the protocol will be assessed by TFS in cooperation with the sponsor. Important deviations from the protocol may lead to exclusion of a subject from the PPS. All such decisions will be made and documented before the trial database is unblinded.

Safety set: All randomised subjects who received at least one dose of the study medication.

Although efficacy summaries will be performed on both the FAS and the PPS, the FAS will be considered the primary analysis population.

Safety summaries will be performed on the safety set.

12.1.2 Definitions

Baseline measurements are defined as last measurement taken before randomisation.

12.1.3 Statistical Issues

Level of Significance, Multiple Comparisons and Multiplicity

For all significance tests, exact p-values (to four decimal places) will be calculated and quoted.

There is one primary efficacy parameter although there are three key secondary efficacy endpoints which are intended to support conclusions based on the primary parameter. In addition, several other endpoints will be considered as descriptive and supportive, and no adjustments for multiplicity will be made for these analyses.

Two comparisons (for the primary and key secondary endpoints) will be carried out. The first will be of once daily dosing vs. placebo and the second will be of intermittent dosing vs. placebo. These two comparisons are not independent of each other and to account for multiplicity, a hierarchical procedure will be used (see below).

See also *Section 12.1.5 Primary Efficacy Analysis*.

Type I Error for Primary and Key Secondary Endpoints

The primary endpoint of (A-a)DO₂ will first be tested for the once daily dosing group versus placebo and, if significant at P<0.05, then the 3 key secondary endpoints will be tested at an overall 5 % significance level using the Hochberg procedure. If the test is significant for all of the key secondary endpoints, then the hierarchical testing will proceed with comparing intermittent dosing vs. placebo for the primary, and then the key secondary, endpoints in the same manner as for once daily dosing vs. placebo.

Full details will be provided in the SAP.

Handling of Dropouts and Missing Data

Different approaches will be used for handling missing data for different endpoints; each is described below for the primary and key secondary endpoints. The efficacy variables will also be analysed using Observed Cases for the PPS.

Adjustment for Covariates

In all analyses of 'change from baseline', the baseline value of the parameter being analysed will be included in an analysis of covariance (ANCOVA) model. The stratification factor 'WLL within 2 months prior to the baseline visit' will be included in all analysis models.

Multicentre Trial

Summary statistics will be performed on the whole populations. For baseline demographics and disease characteristics, primary endpoint, and key secondary endpoints summary statistics will also be performed by centre and for Japan vs. Europe vs. US. Centre will not be included as a stratification factor in either the randomisation procedure or data analysis. All subject listings will be sorted by centre.

Examination of Subgroups

Summary statistics will be presented graphically for the subgroups of subjects having a WLL within 2 months prior to randomisation vs. the subgroup not doing so. Summary statistics will be presented graphically by region and by site. No statistical interaction tests are planned for any of the subgroups.

12.1.4 Summary Statistics

In general, data will be summarised using summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, quartile 1, median, quartile 3 and maximum value. Categorical data will be presented as counts and percentages. The data will be presented by visit. Individual subject data will be listed.

12.1.5 Primary Efficacy Analysis

The primary efficacy variable, (A-a)DO₂, will be tested using an ANCOVA model. This model will have change from baseline to Week 24 in (A-a)DO₂ as the response variable, whilst treatment group, WLL within 2 months prior to randomisation, and baseline (A-a)DO₂ will be predictor variables. The mean difference between each active dose and placebo in change from baseline of (A-a)DO₂ will be estimated, along with its 95% confidence interval (CI) and associated statistical significance test.

Subjects who withdraw from their randomised treatment before week 24 should still be followed up through to week 24. For such patients, their week 24 data will be considered as primary, irrespective of treatment discontinuation, treatment interruption(s), use of rescue

medication (WLL or other), etc. The feasibility and likely meaningfulness of this analysis will be reviewed in the blind review of the SAP, once the extent and pattern of missing data are known.

A sensitivity analysis will include a mixed model for repeated measures including factors for treatment, visit, treatment-by-visit interaction, and baseline (A-a)DO₂.

Subjects who withdraw from the study early and who do not have week 24 data available will have their (A-a)DO₂ measurement imputed using multiple imputation for which full details will be given in the Statistical Analysis Plan. Further sensitivity analyses will include:

- “reasonably worst case” scenario. For the primary analysis, patients in either of the active arms will have the value of the 10th percentile from their dose arm imputed (i.e. approximately the 3rd worst case) whilst patients in the placebo arm will have the median for the placebo arm imputed.
- Tipping point analysis: Patients in any group with a missing endpoint will be assigned progressively worse (A-a)DO₂ to find the point at which the results reverse from favouring the active treatment to the placebo.

All attempts will be made to retain subjects in the trial, even if they wish to withdraw from trial treatment. Hence it is anticipated that there will be only minimal missing (A-a)DO₂ data at week 24 and a further sensitivity analysis will use all available Week 24 data with no imputation (i.e. a “completers” analysis).

12.1.6 Key Secondary Efficacy Analyses

Absolute change from baseline in 6MWD and in SGRQ will be analysed using the same ANCOVA model as for (A-a)DO₂. Imputation for missing data will also follow the same rules as for (A-a)DO₂.

Time to WLL (time from randomisation to documentation that WLL needs to be carried out) will be analysed by the logrank test. The proportion of subjects in each group who require WLL at, or before, week 24 will be estimated, along with a 95% CI for the difference in rates between each active dose and placebo. Subjects who fulfil the criteria for rescue treatment but refuse (or for some other reason do not get) WLL, will be counted as if WLL was conducted. This decision will be documented when the trial is complete in the blind review of the SAP.

In addition, the hazard ratio and its 95% confidence interval will be estimated from a Cox model with covariates treatment, geographic region, and need for WLL within 2 months before randomisation.

Any patient who withdraws from the trial before week 24 and who has not needed a WLL will be considered as censored for the event of WLL. A sensitivity analysis will additionally be performed considering any such patients as having the endpoint event at the time they withdraw. All patients who reach week 24 and have not needed a WLL will be considered censored at week 24.

Further rules for handling missing data will be confirmed at the blind review of the SAP. Assuming that any subjects who withdraw from treatment remain in the trial, the Week 24 data will be considered as primary, regardless of adherence to treatment.

12.1.7 Further Secondary Efficacy Analyses

Analyses of further secondary endpoints will be described in the SAP.

The following tabulations will be presented:

- Number of subjects with >5 mmHg/>0.67 kPa and number of subjects with >10 mmHg/>1.33 kPa improvement in (A-a)DO₂ after 24-weeks treatment
- Number of subjects with >5 percentage points and number of subjects with >10 percentage points improvement in VC (% predicted) after after 24-weeks treatment
- Number of subjects with >10 percentage points improvement in DLCO (% predicted) after 24-weeks treatment
- Number of subjects with >10 percentage points improvement in FEV₁ (% predicted) and FVC (% predicted) after 24-weeks treatment
- Number of subjects with >10% relative improvement in PaO₂ after 24-weeks treatment
- Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 24-weeks treatment
- Number of subjects with improved CT score after 24-weeks treatment

12.1.8 Exploratory Efficacy Analyses

The tabulations for the following exploratory endpoints from the Double-blind period will be presented and the analyses will be described in the SAP:

- Absolute change from baseline of (A-a)DO₂, VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), FVC (% predicted), and relative change from baseline of PaO₂ after 4 and 12-weeks treatment
- Time period during which the (A-a)DO₂ level is maintained below Baseline –10mmHg
- Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 4 and 12-weeks treatment
- Time period during which the improvement in tolerance to exercise is maintained
- Change from baseline in dyspnoea score and cough scores (severity and frequency) after 4 and 12-weeks treatment.
- Number of subjects with improved QoL (change of ≥4 units on the SGRQ/ number of subjects with 'no problems' in EQ-5D), after 4, 12, and 24-weeks treatment
- Change in serum concentration of possible biomarkers; KL-6, CEA, SP-A, SP-B , SP-C, SP-D, Cyfra 21-1 and LDH after 4, 12, and 24-weeks treatment
- Levels of anti-GM-CSF after 4, 12 and 24-weeks treatment
- Change in serum concentration of GM-CSF post first dose of trial drug and after 4-weeks treatment
- Number of subjects in need for oxygen supplement therapy during 24-weeks treatment.
- The distribution of DSS at Screening and at Week 24.
- The percentage of subjects with DSS 1 or 2 at Week 24.

The tabulations for the following exploratory endpoints from the Follow-up period will be presented and the analyses will be described in the SAP:

- Number of subjects requiring WLL, or other treatment for aPAP and number of treatment courses required during 24 or 48-weeks follow-up
- Time to WLL, or other treatment for aPAP during 24 or 48-weeks follow-up
- Absolute change from baseline in (A-a)DO₂ and VC (% predicted), DLCO (% predicted), FEV₁ (% predicted), FVC (% predicted), and relative change from baseline of PaO₂ after 12, 24, 36 and 48-weeks follow-up
- Number of subjects with improved tolerance to exercise (increase in distance walked ≥50 m or desaturation <4 percentage points on the 6MWT) after 12, 24, 36 and 48-weeks follow-up
- Levels of anti-GM-CSF after 12 and 24-weeks follow-up
- The distribution of DSS after 24 and 48-weeks follow-up
- The percentage of subjects with DSS 1 or 2 after 24 and 48-weeks follow-up

Rules for handling missing data for these endpoints, where necessary, will be documented before the trial data are unblinded and when the patterns and extent of missing data are known.

12.1.9 Demographic and Other Baseline Characteristics

Subject disposition, demographic and other baseline data will be presented using summary statistics. Both the FAS and the PPS will be used for this presentation.

12.1.10 Exposure to Treatment

Exposure to treatment will be presented using summary statistics.

12.1.11 Concomitant Treatment

Concomitant medication and concomitant therapy will be summarised as number of subjects being treated with each type of medication/therapy classified according to Anatomical Therapeutic Chemical (ATC) level 3 and WHO Drug Dictionary preferred term. The safety set will be used for this presentation.

12.1.12 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and by preferred term (PT).

The total number of subjects with at least one AE and the total number of AEs will be presented.

The number of subjects and the number of AEs will be tabulated by SOC and by PT.

AEs will also be tabulated versus worst severity and worst relationship to treatment.

12.1.13 Other Safety Assessments

Physical Examination

Physical examination data will be summarised, together with changes from Baseline.

Vital Signs

Vital signs will be summarised, together with changes from Baseline.

ECG

Electrocardiogram parameters (heart rate, QRS, PR and QT intervals) will be summarised, together with changes from Baseline. QTcF will be calculated and be summarised, together with changes from Baseline.

Laboratory Safety Assessments

For laboratory data, summary statistics will be produced for observed values and for changes from Baseline to each visit. Abnormal values will be flagged in listings.

Shift tables will show the number of subjects who changed from below, within or above the reference range at baseline to below, within or above the reference range at end of treatment.

For laboratory values which are below the limit of quantification, the value corresponding to the limit of quantification will be used when summarising data (e.g. if the result is <0.5 then the value 0.5 will be used in the statistical analysis).

12.2 Determination of Sample Size

The trial is a randomised 3-arm trial in which two thirds of the subjects receive active drug and one third receive placebo.

The sample size calculation was based on data in an earlier trial [19], where the mean (and standard deviation) (A-a)DO₂ were 31.3 (7.4) before treatment and 12.9 (7.6) after treatment (all measured in mmHg). It was also based on previous assumptions about how the trial would be analysed (notably, to combine the two active doses together for the primary analysis). The minimum clinically relevant difference to detect between active and placebo arms is considered to be 10-12 mmHg. In order to ensure such an effect size can be detected, a delta of 10 mmHg has been used in the sample size calculation which is based on an unpaired *t*-test of mean difference between the two active arms (combined) vs. placebo, using a significance level of 0.01 and a power of 90%.

The trial will test the null hypothesis

$$H_0: \mu_{\text{diff}} = 0$$

Versus the alternative hypothesis

$$H_1: \mu_{\text{diff}} \neq 0.$$

The calculation was based on an unpaired *t*-test, combining the two active dose groups together and comparing to placebo. Calculations were made using nQuery Advisor® 7.0.

Table 3 Two Group T-Test of Equal Means (Unequal n's)

Test significance level, α	0.010
1 or 2 sided test?	2
Difference in means, $\mu_1 - \mu_2$	10.000
Common standard deviation, σ	7.500
Effect size, $\delta = \mu_1 - \mu_2 / \sigma$	1.333
Power (%)	90
n_1	14
n_2	28
Ratio: n_2 / n_1	2.000
$N = n_1 + n_2$	42

Based on the assumption listed in *Table 3*, above, 42 subjects will be required to be randomised.

Based on an evaluation of variability and plausible effect sizes for the key secondary endpoints, the sample size is increased to 90 subjects (30 patients in each treatment arm), to increase the power to identify statistically significant treatment effects also on one or more of the key secondary endpoints.

Very limited data on these secondary endpoints are available but with a sample size of 30 subjects per group, it would be possible to show a treatment effect of 50 m on the 6MWD (assuming a SD of 50) or of 10 points on the SGRQ (assuming a SD of 10) with approximately 90 % power.

Because of the limited data available, a fully blinded sample size re-estimation procedure will be carried out to assess the standard deviations of the 6MWD and the SGRQ, and the overall event rate of WLL. This will be done in January 2018 when approximately 50 patients will have reached 24 weeks of treatment.

The change from baseline to week 24 in 6MWD [and SGRQ] will be summarised in an ANCOVA model including WLL (stratification), and baseline 6MWD [SGRQ]. For the purposes of the sample size re-estimation process, only data on patients who have baseline and week 24 data will be used and no imputation will be made for missing values. Additionally, the overall (pooled) event rate for WLL will be determined including any patients who meet the criteria for WLL any time prior to week 24, but excluding any patients who withdraw prior to week 24 where WLL has not been required.

Based on a literature review of different pulmonary indications but with main focus on Idiopathic Pulmonary Fibrosis carried out in November 2017 [38, 39, 40], the minimal clinically important effect sizes for 6MWD and SGRQ in aPAP are considered to be in the order of 40-50 m and 7-10 points, respectively. From each ANCOVA model, the respective residual variance for 6MWD [and SGRQ] will be used to calculate sample size based on the effect sizes of 50 m and 10 points, respectively. Similarly, the sample size for comparing WLL rates of 5% (active) versus 20% (placebo) at 24 weeks will be checked, based on the observed (pooled) WLL rate. All calculations will be made based on a 2-sided 5% significance level, and 80% and 90% power.

If the maximum of these sample size calculations comes to no more than 33 patients per group, then no change to the target sample size will be made. Otherwise, the sample size will be increased to attain 90% power for at least 2 of the 3 key secondary endpoints, subject to the total study size not exceeding 150 patients.

The results of the sample size re-estimation will be documented in a report.

12.3 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Any deviation(s) from the original statistical analysis plan (as described in the trial protocol or in the SAP) will be described and justified in a protocol amendment and/or in a revised SAP and/or in the final report, as appropriate.

12.4 Interim Analysis

No interim analyses are planned for this clinical trial.

13 INVESTIGATOR/SPONSOR RESPONSIBILITIES

13.1 Ethics

13.1.1 Independent Ethics Committee (IEC) / Institutional Review board (IRB)

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

13.1.2 Ethical Conduct of the Trial

The trial will be conducted in compliance with the protocol, 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.

13.1.3 Subject Information and Consent

All subjects will receive written and verbal information regarding the trial at a prior meeting. This information will emphasise that participation in the trial is voluntary and that the subject may withdraw from the trial at any time and for any reason. All subjects will be given the opportunity to ask questions about the trial and will be given sufficient time to decide whether to participate in the trial.

Before any trial-related procedures, the informed consent form will be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

The consent includes information that data will be recorded, collected, processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the trial.

A copy of the subject information including the signed consent form will be provided to the subject.

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 during the trial period
- Any information relating to AEs

- All treatments and medications prescribed/administered (including dosage)
- Date of trial termination
- 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 Access to Source Data and Documentation

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

13.4 Monitoring

The monitor will visit the trial site to ensure that the trial is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any trial specific documents such as monitoring manual and eCRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the trial protocol
- Informed consent has been obtained from all participants
- AEs have been reported as required
- Data are being accurately recorded in the eCRFs
- IMP is being stored correctly and drug accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the trial

The investigator and the site are receiving sufficient information and support throughout the trial

Moreover, during monitoring visits the data recorded in the eCRFs, source documents and other trial-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the subject in the trial i.e. source data verification.

13.5 Data Management

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

An eCRF system, Trial-on-Line, 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 Trial-on-Line and/or the TFS Data Management Team. The data will be subjected to validation according to TFS SOPs 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.

13.6 Quality Assurance and Audit

Audits or inspections, including source data verification, may be performed by representatives of TFS, the sponsor, a CA and/or an IEC.

13.7 Record Retention

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.

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.

13.8 Protocol Deviations

Deviations to the trial protocol will be documented in a Protocol Deviation Log.

The classification of subjects into protocol deviators will be made during a meeting before database lock. The classification will be mutually agreed between the sponsor and TFS before breaking the randomisation codes. Listings will indicate the allocation of subjects by analysis set and the number of subjects per analysis set will be recorded in the clinical trial report.

13.9 Insurance

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

13.10 Report and Publication

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

Two Clinical Trial Reports (CTRs) will be prepared according to the ICH Guideline for Structure and Content of Clinical Trial Reports (ICH E3). After the last subject has completed the 24-week Double-blind treatment period a CTR detailing the results of double-blind treatment will be produced. The results for the Follow-up period will be reported separately.

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 multicentre study may publish data subsets from their individual institution only after publication of the primary manuscript. A 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 [41] 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.

14 REFERENCE LIST

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41. Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2017), available from <http://clinicaltrials.ifpma.org/resource-centre/clinical-trials-position-papers>

15 APPENDICES

- Appendix A:** St Georges Respiratory Questionnaire (SGRQ) UK/ English
(6 pages) (original) version,
- Appendix B:** EuroQol-5D (EQ-5D-5L) questionnaire. English version (3 Pages)
- Appendix C:** Borg CR10 Scale. Borg GA. Psychophysical bases of perceived perception. Med Sci Sports Exerc 1992;14:377-381.
- Appendix D:** Cough Questions