SAV006-03

An open-label, non-controlled, multicentre clinical trial of inhaled molgramostim in autoimmune pulmonary proteinosis patients

NCT03482752

Clinical Trial Protocol

Version 5.0

24 August 2018

MOLGRAMOSTIM NEBULISER SOLUTION

CLINICAL TRIAL PROTOCOL
SAV006-03

AN OPEN-LABEL, NON-CONTROLLED, MULTICENTRE CLINICAL TRIAL OF INHALED MOLGRAMOSTIM IN AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS PATIENTS

IMPALA EXTENSION TRIAL

Product Name:	**Molgramostim Nebuliser Solution (Molgradex®) 300 µg**
Indication:	**Autoimmune Pulmonary Alveolar Proteinosis**
Phase:	**III**
EudraCT No.	**2017-004078-32**
Sponsor:	**Savara ApS Slotsmarken 17, 2 t.v. 2970 Hørsholm Denmark**
Date of Protocol:	**24-Aug-2018**
Version:	**Final version 5.0 (All countries)**

1. SYNOPSIS

Name of Sponsor/Company:
Savara ApS

Name of Investigational Product:
Molgramostim Nebuliser Solution (Molgradex®)

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

Title of Study:
An open-label, non-controlled, multicentre clinical trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis patients

Study center(s): Centres participating in the IMPALA (MOL-PAP-002) trial

International Coordinating Investigator: Francesco Bonella, MD, PhD (Interstitial and Rare Lung Disease Unit, Ruhrlandklinik University Hospital, Essen, Germany)

Studied period (years):	**Phase of development:** III
Estimated date first subject enrolled: Q1 2018 Estimated date last subject completed: Q4 2021	

Objectives:

Primary:

- To investigate safety of long term use of inhaled molgramostim.

Secondary:

- To investigate effects of long term use of inhaled molgramostim on oxygenation.
- To investigate effects of long term use of inhaled molgramostim on exercise capacity.
- To investigate effects of long term use of inhaled molgramostim on respiratory quality of life.
- To investigate requirement for whole lung lavage (WLL) during long term use of inhaled molgramostim.
- To investigate effects of long term use of inhaled molgramostim on lung function.
- To investigate maintenance of effect after discontinuation of inhaled molgramostim.

Methodology:

Subjects with autoimmune pulmonary alveolar proteinosis (aPAP) who have completed the IMPALA trial will be eligible for the trial.

At the Baseline visit, eligible subjects may continue or re-start treatment with inhaled molgramostim (300 μg) administered intermittently in cycles of seven days molgramostim, administered once daily, and seven days off treatment.

Trial visits will be conducted at 6-monthly intervals until the end of trial. Participating subjects will be encouraged to contact the clinic between visits if they experience adverse events (AEs) or worsening of aPAP, or if they have any other concerns.

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 hypoxaemia or desaturation, according to the investigator's judgement. The reason(s) for conducting WLL will be documented. Subjects undergoing WLL will continue treatment with molgramostim, unless discontinuation is medically required, according to investigator's discretion.

Subjects may discontinue molgramostim due to remission of aPAP, lack of response that requires a different treatment modality, or AEs. Subjects becoming pregnant will be required to discontinue treatment with molgramostim. Subjects who discontinue molgramostim will continue in the trial and attend visits according to the same schedule until end of the trial. Molgramostim treatment may be re-started if medically required. Subjects not requiring treatment at the Baseline visit may start molgramostim treatment during the trial if medically required.

Number of subjects (planned):
Up to 90 subjects may be included.

Diagnosis and main criteria for inclusion:
Inclusion Criteria:

1. Completer of the IMPALA trial.
2. 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 where inhibition of ovulation is the primary mode of action, 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 urine pregnancy test at Baseline, or at start of treatment if treatment is not dispensed at Baseline, and must not be lactating during and until 30 days after last dose of trial treatment*.
3. 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.
4. Willing and able to provide signed informed consent.

* Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the female trial participant of child bearing potential and that the vasectomised partner has received medical assessment of the surgical success. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

Exclusion criteria:

1. Treatment with Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) products other than molgramostim nebuliser solution within three months of Baseline.
2. Treatment with any investigational medicinal product other than inhaled molgramostim within four weeks of Baseline.
3. History of allergic reactions to GM-CSF.
4. 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.
5. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product.
6. History of, or present, myeloproliferative disease or leukaemia.
7. Apparent pre-existing concurrent pulmonary fibrosis.
8. Any other serious medical condition which in the opinion of the investigator would make the subject unsuitable for the trial.

Investigational product, dosage and mode of administration:

Investigational Medicinal Product (IMP): Molgramostim nebuliser solution

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

Pharmaceutical form: Nebuliser solution

Route of administration: Inhalation

Inhalation device: PARI eFlow (PARI Pharma GmbH)

Duration of treatment:

The total duration of the treatment is up to three years from first subject first visit. Should the product not have obtained marketing authorization at this date, the trial will be amended with an extension of one year at a time to ensure adequate treatment options for subjects in the trial who still are in need of treatment with inhaled molgramostim.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Primary Endpoints

- Number of AEs, serious adverse events (SAEs), adverse drug reactions (ADRs), and AEs leading to treatment discontinuation during the trial.

Secondary Endpoints:

- Alveolar-arterial oxygen difference ((A-a)DO_2) during the trial.
- 6-minute walking distance (6MWD) during the trial.

- St Georges Respiratory Questionnaire (SGRQ) total score during the trial.
- Frequency of WLL during the trial.
- Diffusion Capacity of the Lung for Carbon Monoxide (DLCO), Forced Expiratory Volume in one second (FEV_1), and Forced Vital Capacity (FVC) during the trial, all expressed as percent predicted.
- Arterial oxygen tension (PaO_2) and disease severity scores (DSS) during the trial.
- Need for oxygen supplement therapy during the trial.
- Number of subjects not requiring treatment for aPAP and time off treatment after discontinuation of inhaled molgramostim

Exploratory Endpoints:

- GM-CSF levels before and 2 hours after dosing

Methods of Assessment:

Lung function variables – DLCO and spirometry (FEV_1 and FVC) will be done in accordance with European Respiratory Society/American Thoracic Society (ERS/ATS) guidance using local equipment. For spirometry percent of predicted values will be calculated centrally using standard equations.

6-minute walking test (*6MWT)* – will be performed in accordance with European Respiratory Society/American Thoracic Society (ERS/ATS) guidance. Borg CR10 scale will be used to assess dyspnoea before and after the test.

Quality of Life score – SGRQ

Laboratory analyses – Local laboratories will be used for analysis of haematology, clinical chemistry and pregnancy testing.

(**For Italy only**: samples will be collected for pharmacokinetic (PK) analysis at Visit 1-6, pre-dose and 2 hours post dosing)

Statistical methods:

Data from the trial will be analysed descriptively. Data from the trial is planned to be combined with relevant data from the IMPALA trial; these combined analyses will be reported separately.

Table 1: Study Flow Chart

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**FU TC**	**Unscheduled**
	Baseline [a]	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**2 wks after trial completion**	
Time	**0**	**Week 26**	**Week 52**	**Week 78**	**Week 104**	**Week 130**	**Week 156**		
Visit Window	N/A	± 4wks	± 4 wks	± 4 wks	± 4 wks	± 4 wks	± 4 wks	+ 1 wk	
Informed consent	X								
Eligibility criteria	X								
Demographics	X								
Concomitant medication	X	X	X	X	X	X	X		X
WLL information [b]	X	X	X	X	X	X	X		X
Pregnancy test and contraceptive check [c]	X	X	X	X	X	X	X		(X)[d]
Physical Exam	(X)		X		X		X		(X)[d]
Vital signs	(X)	X	X	X	X	X	X		(X)[d]
ECG	(X)	X	X	X	X	X	X		(X)[d]
Blood gas analysis [e]	(X)	X	X	X	X	X	X		(X)[d]
Lung function tests [f]	(X)	X	X	X	X	X	X		(X)[d]
6MWT [g]	(X)	X	X	X	X	X	X		(X)[d]
Quality of Life (SGRQ)	(X)	X	X	X	X	X	X		
DSS	(X)	X	X	X	X	X	X		(X)[d]
Overall Clinical Assessment	X	X	X	X	X	X	X		X
CT Scan	(X)[d]	(X)[d]	(X)[d]	(X)[d]	(X)[d]	(X)[d]	(X)[d]		(X)[d]

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**FU TC**	**Unscheduled**
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Time	**0**	**Week 26**	**Week 52**	**Week 78**	**Week 104**	**Week 130**	**Week 156**		
Visit Window	N/A	± 4wks	± 4 wks	± 4 wks	± 4 wks	± 4 wks	± 4 wks	+ 1 wk	
Laboratory Safety Analyses [h]	(X)	X	X	X	X	X	X		(X) [d]
AEs	X	X	X	X	X	X	X	X	X
PK samples (**Italy only**) [i]	X	X	X	X	X	X			
Medical history	X								
Dispense trial drug [j]	X	X	X	X	X	X			(X) [d]
Subject Diary Card [k]	X	X	X	X	X	X	X		
Compliance		X	X	X	X	X	X		(X) [d]
Study continuation or termination [l]		X	X	X	X	X	X		(X) [d]

Notes: See next page.

FU = follow-up, TC = telephone call, WLL = whole lung lavage

[a] Baseline (Visit 1) may coincide with the final visit of the IMPALA (MOL PAP 002) trial; if so, assessments performed at Visit 11 (for subjects enrolled under protocol MOL PAP 002 version 4.0 or later), or Visit 13 (subjects enrolled under a protocol version prior to version 4.0) may serve as the baseline assessments for this protocol. If more than 3 months have elapsed since completion of the IMPALA study to Baseline (Visit 1) the assessments must be repeated.

[b] Requirement for WLL and if required, indication for procedure will be recorded. If WLL is performed date of WLL and type of WLL (unilateral, bilateral) will be recorded.

[c] Serum pregnancy test at Baseline (Visit 1) and at all subsequent visits during treatment with inhaled molgramostim (pregnancy tests for subjects not receiving trial drug are not mandatory). A urine pregnancy test will also be performed at dosing at Baseline (Visit 1) to immediately confirm that the subject is not pregnant and meets the inclusion criterion for treatment. If treatment is not dispensed at Baseline (Visit 1) the urine pregnancy test will instead be performed at the first visit treatment is dispensed. Subjects will be requested to do monthly urine testing at home during treatment.

[d] Only applicable if assessment is done according to clinical practice or medical need, e.g. in case of a clinical deterioration. If done, results will be recorded

[e] Capillary sampling for blood gas analysis may be used instead of an arterial blood gas sample at sites that routinely use this method.

[f] DLCO, FEV_1, and FVC (absolute values and % of predicted values).

[g] 6MWT includes assessment of SpO_2 and Borg CR10 score for dyspnoea before, during (SpO_2) and after (Borg) the test. If the subjects used supplemental O_2 during the procedure in IMPALA, the same O_2 flow will be used at the subsequent tests in this trial, if possible.

[h] Haematology and clinical chemistry

[i] For Italy only: Patients will have their visits scheduled for an on-treatment week within the allowed window of +/- 4 weeks. The first sample must be taken just prior to inhalation of molgramostim. The 2nd sample must be taken 2 hours post dosing, (+/- 10 minutes). See Section 10.8.5.1

[j] Trial drug is dispensed to subjects who require treatment according to investigator's discretion. **For Italy only**: The visit should take place in during the week on treatment. On the day of dosing, the subjects will do the nebulization at the clinic, in order to collect pre-dose PK sample.

[k] 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 they have experienced, enter dates for pregnancy tests taken at home (if applicable) and dates for changing of the nebuliser mouthpiece in the subject diary.

[l] If the planned trial termination has been declared since the subject's last visit in the trial, the subject will leave the trial.

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

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LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6MWD	6 Minute Walk Distance
6MWT	6 Minute Walk Test
(A-a)DO_2	Alveolar-arterial Oxygen Difference
aPAP	Autoimmune Pulmonary Alveolar Proteinosis
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Concentration versus Time Curve
BAL	Broncho-alveolar Lavage
Cmin	Minimum Measurable Plasma Concentration
Cmax	Maximum Measurable Plasma Concentration
CRO	Clinical Research Organisation
CRP	C-Reactive Protein
CT	Computed Tomography
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
EFD	Embryo-foetal Developmental
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor

Abbreviation or Specialist Term	Explanation
GMP	Good Manufacturing Practice
HEENT	Head, eyes, ears, nose and throat
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review board
MAD	Multiple Ascending Dose
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MRC	Medical Research Council
NOAEL	No Observed Adverse Effect Level
PaO_2	Arterial Oxygen Tension
PAP	Pulmonary Alveolar Proteinosis
PAS	Periodic Acid-Schiff
PK blood sample	Pharmacokinetic blood sample
PT-INR	Prothrombin Time International Normalised Ratio
QoL	Quality of Life
RBC	Red Blood Cell
RDW	Red Blood Cell Distribution Width
rhGM-CSF	Recombinant Human Granulocyte Macrophage Colony Stimulating Factor
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SGRQ	St Georges Respiratory Questionnaire
SOP	Standard Operating Procedure
SpO_2	Oxygen Saturation (indirect measurement)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Telephone Call
TLC	Total Lung Capacity

Abbreviation or Specialist Term	Explanation
VC	Vital Capacity
WBC	White Blood Cell
WLL	Whole Lung Lavage

4. INTRODUCTION

4.1. Background

Pulmonary alveolar proteinosis (PAP) is a rare autoimmune disease with an estimated prevalence of 0.7 per 100,000 individuals [Trapnell 2014]. It is characterised by high levels of autoantibodies against Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) in alveoli and blood. The autoantibodies neutralise the normal biologic action of GM-CSF in the lungs [Khan 2012]. 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 [Trapnell 2014, Rosen 1958, Trapnell 2003, Inoue 2008]. 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 [Trapnell 2003, Inoue 2008].

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 anaesthesia 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 [Dranoff 1994].

Investigational Medicinal Product (IMP)

The IMP, molgramostim nebuliser solution, is developed by Savara Pharmaceuticals. The drug substance molgramostim (rhGM-CSF) is produced in *E. coli* and has the same amino acid sequence as the native protein but is not glycosylated. Another rhGM-CSF product, sargramostim, which is produced in *S. cerevisiae* slightly differs from native GM-CSF by having one amino acid difference in position 23 and is glycosylated. Production of molgramostim in bacteria circumvents the variability in the molecular weight seen in sargramostim. The formulation currently under development is intended for inhalation use. No rhGM-CSF products have been approved for respiratory disease therapy or for inhalation use in any indication.

Two rhGM-CSF products for systemic use have been approved, *E. coli* derived molgramostim (Leucomax®) and yeast-derived sargramostim (Leukine®), largely for use following chemotherapy and/or bone marrow transplantation to reduce the risks of neutropenia such as infection, or in case of graft failure after bone marrow transplantation. Published clinical studies of relevance to the development of molgramostim nebuliser solution in which investigational or commercially available

rhGM-CSF products have been administered are summarised and discussed in the Investigator's Brochure (IB).

Pre-clinical studies in cynomolgus monkeys show that molgramostim nebuliser solution is well tolerated locally and that it has low systemic toxicity. The small fraction of the inhaled dose that is absorbed systemically causes increases in stem cell proliferation, resulting in increased number of monocytes, eosinophils and neutrophils in the circulation; similar to the known effects after intravenous administration of rhGM-CSF. Local effects in the lungs are characterised by accumulation of inflammatory cells, mostly macrophages, accompanied by an increased cellularity in the lymphoid tissue that is associated with the respiratory tract and minimal to mild exudation of red blood cells (RBC) into the alveoli. The infiltration of inflammatory cells was not associated with any signs of inflammation or impaired lung function, and it is interpreted as an exaggerated pharmacological effect of molgramostim. Its severity was graded slight at the 10 µg/kg/day dose level and moderate above this level. Duration of treatment did not affect the severity of this finding. Reduced severity of the lung and tracheobronchial changes following 4 weeks off dose in recovery animals suggests partial resolution of the changes.

An embryo-foetal developmental (EFD) toxicity trial in rabbits revealed increases in post implantation loss, decreases in the number of live implants, effects on sex ratio and a slight increase in the incidence of major malformations in foetuses at the highest dose (150 µg/kg/day). Studies in sexually mature monkeys have shown that molgramostim has no effect on male and female reproductive organs. Further details are available in the IB. The nonclinical data raises a concern about human teratogenicity/fetotoxicity in early pregnancy, risk mitigation measures (contraception and pregnancy testing) have therefore been implemented in the trial.

The first clinical trial with molgramostim nebuliser solution has been completed (MOL-001). This was a phase I trial to investigate the effects of molgramostim nebuliser solution in healthy adult subjects. The trial was a randomised, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) trial 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 trial. GM-CSF was not measurable in serum before trial drug administration. In the SAD part, GM-CSF was absorbed into systemic circulation with time of maximum plasma concentration (t_{max}) of 2 hours after inhalation of molgramostim 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 maximum measurable plasma concentrations (C_{max}) ranged between 9.1 and 41 pg/mL. C_{max} was similar for the 300 and 600 µg dose levels. In the MAD part, despite the short half-life of approximately 4 hours where GM-CSF levels returned to

levels below quantification limits after each dose, there was evidence of some accumulation after multiple dosing. C_{max} increased from 32 pg/mL on Day 1 to 90 pg/mL on Day 6 for the 300 µg dose level and from 96 pg/mL to 251 pg/mL from Days 1 to 6 for the 600 µg dose level. Likewise, AUC_{last} increased from 97 to 248 pg•h/mL from Days 1 to 6 for the 300 µg dose level and from 350 to 802 pg•h/mL for the 600 µg dose level. Minimum measurable plasma concentrations (C_{min}) on Day 6 were 3.6 and 5.1 pg/mL measured at 8 and 12 hours, respectively for the 300 and 600 µg dose levels.

Changes in white blood cells (WBC) and differential counts were in line with the mode-of-action of GM-CSF and these were not clinically significant in most subjects. In subjects treated with molgramostim 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).

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 was 48 in 30 subjects in the combined molgramostim groups and 15 in 12 subjects in the placebo groups. A higher number of treatment-related AEs were observed in the 600 µg dose level compared to the 300 µg dose level and placebo in the MAD part. There was no development of anti-drug antibodies up to 28 days after last dose. There were no serious adverse events (SAEs), severe AEs, dose-limiting toxicity, or other remarkable findings of clinical concern from review of clinical safety data. Further details are available in the IB.

Study MOL-PAP-002, the IMPALA trial, is a pivotal clinical trial in aPAP being conducted in Europe, Australia, Israel, Japan, Russia, South Korea, Turkey, and the US. This is a randomised, double-blind, placebo-controlled trial, with an open-label follow-up, in which it is planned to enroll 135 patients with aPAP. Double-blind treatment consists of daily administration of either molgramostim nebuliser solution 300 µg, or alternating cycles of molgramostim nebuliser solution 300 µg daily for seven days and placebo daily for seven days, or daily administration of placebo for 24 weeks during the double-blind period. After the double-blind period, there is a 24- to 48-week follow-up period, during which open-label treatment with molgramostim nebuliser solution is given using an intermittent dosing regimen (molgramostim nebuliser solution 300 µg daily for seven days, then seven days off treatment). Unblinded safety data are reviewed by an independent data safety monitoring board (DSMB) at 6-monthly intervals. The review in April 2018 included 96 randomised patients. Data reviewed comprised AEs, safety laboratory data, vital signs and pulmonary function tests up to Visit 13 (24 weeks double-blind treatment and 48 weeks of follow-up). No safety signals of concern were identified and the DSMB recommended that the trial could continue as planned. Further details are available in the IB.

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 [Khan 2012].

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)DO_2) 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 [Tazawa 2010]. A reduction of 12.6 mmHg at rest ($p=0.00003$) and 20 mmHg at exercise from 12 patients was reported in another trial [Wylam 2006] and a recent trial [Papiris 2014] reported a mean decrease of 17.4 mmHg ($p=0.031$). Patients also experienced improvement in dyspnoea, 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 in one second (FEV_1), 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 [Morgan 2009] All five patients were able to discontinue supplemental oxygen. The results from these studies indicate an improvement that remains present for more than one year after treatment has been discontinued [Tazawa 2010, Wylam 2006].

Data are available from eight aPAP patients in which molgramostim products other than molgramostim nebuliser solution have been administered via inhalation [Tazawa 2005, Yamaguchi 2012, Ohashi 2012, Yu 2014]. The treatment duration for all patients was 24 weeks or more. Three different treatment regimens were 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)DO_2 was reported for the three patients included [Tazawa 2005]. In another trial, a decrease in (A-a)DO_2 by more than 10 mmHg was reported in two out of four patients, improved vital capacity (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 [Yamaguchi 2012]. 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 (PaO_2) of 68 mmHg on room air as well as significant improvement in chest CT [Yu 2014]. More details about the clinical studies and case reports using inhaled rhGM-CSF are available in the IB.

4.2. Rationale

The current trial is an open-label extension trial to the Phase 3 IMPALA trial (MOL-PAP-002) to allow patients to continue treatment with inhaled molgramostim nebuliser solution, and to investigate long term safety and efficacy of inhaled molgramostim nebuliser solution in aPAP patients. The trial consists of an up to 36-month treatment period during which patients will receive the same dose regimen of inhaled molgramostim nebuliser solution as was used in the Follow-up Period of the IMPALA trial (cycles of seven days molgramostim 300 µg administered once daily, and seven days off treatment). The patient population to be included in the current trial will be patients with aPAP who have completed the IMPALA trial.

The primary objective is safety assessed by AE reporting. In addition to clinical signs and symptoms, clinically significant changes in laboratory parameters (haematology and clinical chemistry) and electrocardiogram (ECG) variables will be reported as AEs. In order to characterize potential systemic adverse effects, GM-CSF levels before dosing and at T_{max} (2 hours) will be assessed in a subset of subjects, i.e. subjects enrolled at the trial site in Italy.

Long term efficacy will also be assessed using (A-a)DO_2, as a secondary endpoint, 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 II trial the statistically significant improvement in (A-a)DO_2 was accompanied by statistically significant improvements in dyspnoea, need for oxygen supplement, walking distance and minimal oxygen saturation (SpO_2) on the 6MWT, VC and DLCO [Tazawa 2010]. Improvements were also associated with morphologic changes as evidenced by statistically significant correlations between high-resolution CT scores and (A-a)DO_2, PaO_2 and DLCO both before and after treatment.

Whilst (A-a)DO_2 is a calculated biomarker, other secondary endpoints focus on important direct clinical outcomes such as the need for WLL and the effect of treatment on exercise capacity, and QoL. 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 [Leth 2013] 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 walking distance (6MWD) and the total score on the St Georges Respiratory Questionnaire (SGRQ) were chosen as secondary endpoints, although data on these endpoints in aPAP are still limited. In addition, pulmonary function, PaO_2 and disease severity, need for oxygen supplement therapy, and number of subjects not requiring treatment and the time off treatment after discontinuation will assessed as secondary endpoints.

4.3. 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 [Seymour 2002, Luisetti 2010].

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 [Ohashi 2012, Leth 2013].

Patients with aPAP have been treated with up to 500 µg/day of inhaled rhGM-CSF for up to 68 months without chronic toxic effects [Papiris 2014, Wylam 2006]. 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 intravenous administration of molgramostim. No severe, serious or dose-limiting AEs were observed in the first clinical trial in humans (MOL-001). The most common AE was cough, which was reported at a similar incidence for 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. In the ongoing IMPALA trial in patients with aPAP, three reviews of unblinded safety data by an independent DSMB have not identified safety signals of concern and the DSMB recommended that the trial could continue as planned.

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 treatment should be discontinued if significant worsening occurs. If there is significant systemic exposure, haematologic findings such as leukocytosis and neutrophilia may occur. As non-clinical data 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 at each trial visit where molgramostim is dispensed and at home at monthly intervals during treatment.

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.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective is to investigate safety of long term use of inhaled molgramostim.

5.2. Secondary Objectives

The secondary objectives are

- To investigate effects of long term use of inhaled molgramostim on oxygenation.
- To investigate effects of long term use of inhaled molgramostim on exercise capacity.
- To investigate effects of long term use of inhaled molgramostim on respiratory quality of life.
- To investigate requirement for WLL during long term use of inhaled molgramostim.
- To investigate effects of long term use of inhaled molgramostim on lung function.
- To investigate maintenance of effect after discontinuation of inhaled molgramostim.

5.3. Study Endpoints

5.3.1. Primary Endpoints

Number of AEs, SAEs, adverse drug reactions (ADRs), and AEs leading to treatment discontinuation.

5.3.2. Secondary Endpoints

- (A-a)DO_2 during the trial
- 6MWD during the trial
- SGRQ total score during the trial
- Frequency of WLL during the trial
- DLCO (% predicted), FEV_1 (% predicted), and FVC (% predicted) during the trial
- PaO_2 and disease severity score (DSS) during the trial
- Need for oxygen supplement therapy during the trial
- Number of subjects not requiring treatment for aPAP and time off treatment after discontinuation of inhaled molgramostim

5.3.3. Exploratory Endpoints

- GM-CSF levels before and 2 hours after dosing

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Subjects with aPAP who have completed the IMPALA (MOL-PAP-002) trial will be eligible for this trial.

At the Baseline visit, eligible subjects may continue or re-start treatment with inhaled molgramostim (300 µg) administered intermittently in cycles of seven days molgramostim, administered once daily, and seven days off treatment.

Trial visits will be conducted at 6-monthly intervals until the end of trial. Participating subjects will be encouraged to contact the clinic between visits if they experience AEs or worsening of aPAP, or if they have any other concerns.

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 will continue treatment with molgramostim, unless discontinuation is medically required, according to investigator's discretion.

Subjects may discontinue molgramostim due to remission of aPAP, lack of response that requires a different treatment modality, or AEs. Subjects becoming pregnant will be required to discontinue treatment with molgramostim. Subjects who discontinue molgramostim will continue in the trial and attend visits according to the same schedule until end of the trial. Molgramostim treatment may be re-started if medically required. Subjects not requiring treatment at the Baseline visit may start molgramostim treatment during the trial if medically required.

6.1.1. Trial Period

The first patient will be included in the trial in Q1 2018 and the expected end of trial is in Q1 2021. Should the product not have obtained marketing authorization at this date, the trial will be amended with an extension of one year at a time to ensure adequate treatment options for subjects in the trial who still are in need of treatment with inhaled molgramostim. Trial completion, defined as the date of the Clinical Trial Report, is expected 1 year after trial end.

6.1.2. End of Trial

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

6.2. Number of Subjects

Up to 90 subjects may be included.

6.3. Treatment Assignment

All subjects in need of treatment will receive inhaled molgramostim.

6.4. Dose Adjustment Criteria

6.4.1. Safety Criteria for Adjustment or Stopping Doses

Not applicable.

6.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

6.5. Criteria for Study Termination

The investigator or the sponsor may terminate this trial prematurely for any reasonable cause. The Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and Competent Authorities 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.
- Marketing approval of molgramostim nebuliser solution.

If the Competent Authority obtains information that raises doubts about the safety or scientific validity of the clinical trial, the Competent Authority can suspend or prohibit the trial. Before the Competent Authority 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.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Completer of the IMPALA trial.
2. 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 where inhibition of ovulation is the primary mode of action, 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 urine pregnancy test at Baseline or at start of treatment if treatment is not dispensed at Baseline, and must not be lactating during and until 30 days after last dose of trial treatment.
3. 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.
4. Willing and able to provide signed informed consent.

* Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the female trial participant of child bearing potential and that the vasectomised partner has received medical assessment of the surgical success. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. [CTFG 2014]

7.2. Subject Exclusion Criteria

1. Treatment with GM-CSF products other than molgramostim nebuliser solution within three months of Baseline.
2. Treatment with any IMP other than inhaled molgramostim within four weeks of Baseline.
3. History of allergic reactions to GM-CSF.
4. 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.
5. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product.
6. History of, or present, myeloproliferative disease or leukaemia.
7. Apparent pre-existing concurrent pulmonary fibrosis.
8. Any other serious medical condition which in the opinion of the investigator would make the subject unsuitable for the trial.

7.3. Subject Withdrawal Criteria

7.3.1. Discontinuation of Trial Treatment

Subjects may be discontinued from treatment and assessments at any time, if deemed necessary by the investigator. Potential reasons for discontinuation of treatment are:

- Remission of aPAP
- Lack of efficacy/worsening of disease (e.g. loss of response that requires a different treatment modality).
- Unacceptable AE (including serious hypersensitivity reaction).
- Pregnancy.

Those who discontinue treatment will not automatically be withdrawn from the trial but will be encouraged to continue to follow the same visit schedule. If medically indicated and no safety-related exclusion criteria have emerged, treatment may be restarted at a later visit.

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

Subjects who fulfil the criteria for rescue treatment will be scheduled for a WLL as described in Section 10.2. Subjects receiving a WLL should continue treatment and attend the remaining visits, unless discontinuation is medically required, according to investigator's discretion.

7.3.2. Withdrawal from the Trial

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

- 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 eCRF (e.g. lost to follow-up, consent withdrawn, AEs, etc.). If a subject is withdrawn from the trial, the investigator should attempt to complete all required trial assessments.

All AEs should be followed-up according to Section 10.9.2.4.

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

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

Table 3: Investigational Product

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

8.2. Prohibited Treatments

Therapy associated with significant immunosuppression is not allowed (e.g. more than 10 mg/day systemic prednisolone) while the subject is treated with IMP. Other rhGM-CSF products are not allowed within three months of Baseline and during the trial.

8.3. Treatment Compliance

Subject compliance 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. If IMP compliance is less than 80% or more than 100 %, the investigator should discuss the reason and educate the subject to comply with protocol.

8.4. Randomisation and Blinding

Not applicable.

8.5. 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. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

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

9.2. Study Drug Packaging and Labeling

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

Individual medication kits containing trial medication for a 26-week treatment period (i.e. 13 weeks of treatment) 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.

9.3. Study Drug Storage

The IMP must be stored at 2-8°C.

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

The IMP kits will be dispensed to the subject at each clinic visit where treatment is required, according to Investigator's discretion, from Baseline through to the penultimate visit.

Subjects will be instructed to store the kit at 2-8°C in a safe and secure place out of the reach of children and protected from light. 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.

9.4. Study Drug Preparation

Not applicable.

9.5. Administration

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.

The subject will administer the first dose of IMP at the Baseline visit (Visit 1) under the supervision of trial personnel, unless they have already dosed within the IMPALA trial on the same day, and will be retrained in IMP administration and medical device maintenance procedure, if required.

For Italy only:

Visits 1 to 6 must be placed in a week on treatment. At the day of the visit, the subject will administer the dose at the clinic, after collection of the pre-dose PK sample.

9.6. Study Drug Accountability

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

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

9.7. Study Drug Handling and Disposal

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

10. STUDY PROCEDURES AND ASSESSMENTS

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

10.1. Written Informed Consent

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

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

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

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

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

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

10.2. Concomitant Treatments

The subject's use of all concomitant medication must be recorded in the eCRF. The use of concomitant medicines should be kept at a minimum and should be kept as stable as possible. Standard information about the medication will be collected including the name of medication, dose, frequency, administration route and treatment period.

Information about WLL performed and oxygen supplementation will be recorded on a specific form in the eCRF.

10.3. Medical History

Medical history assessment will be assessed at Baseline (Visit 1).

AEs that occurred during previous treatment with inhaled molgramostim, were reported as AEs in IMPALA, and are still ongoing, will be recorded as medical history. AEs that occurred after completion of IMPALA but still had a reasonable time-relationship to inhaled molgramostim treatment, and were not reported in IMPALA, and are still ongoing, will be reported as AEs at Baseline (Visit 1).

10.4. Demographics

Demographic information including date of birth, age, height, weight sex and race will be entered in the eCRF.

10.5. Subject Diary

The subject will receive a subject diary at the timepoints shown in Table 1. The subject will be asked to record the following information in the subject diary:

- AEs experienced between the visits
- Dates for changes of the nebuliser mouthpiece. The site should enter the expected dates for changing the nebuliser mouthpiece.
- Dates for taking pregnancy tests at home (if applicable). The site should enter the expected dates for taking the pregnancy tests.
- The subjects will also be asked to place the tear-off label from the IMP box in the subject diary.

10.6. Follow-up Telephone Visit

The site should call the subject approximately one week after the subject has completed the last trial visit in order to assess whether any new AEs have occurred after the visit, and to obtain follow-up information on any AE ongoing at the last trial visit.

10.7. Efficacy Assessments

10.7.1. Blood Gas Analysis

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

- PaO_2 (mmHg/kPa) – arterial partial pressure of oxygen
- $PaCO_2$ (mmHg/kPa) – arterial partial pressure of carbon dioxide
- F_iO_2 – fraction of inspired oxygen

P_{atm} (ambient atmospheric pressure) must be collected using a bedside barometer. The P_{H2O} (saturated vapour pressure of water at body temperature) will be set to 47 mmHg / 6.266 kPa.

The Aa Gradient $(A\text{-}a)DO_2$ will be calculated centrally using the following formula:

$$Aa\ Gradient = \left(F_iO_2(P_{atm} - P_{H_2O}) - \frac{P_aCO_2}{0.8}\right) - P_aO_2$$

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.

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 should be conducted with the subject breathing room air. If the subject cannot tolerate temporary discontinuation of supplemental oxygen during blood gas sampling, blood gas sampling at subsequent visits should, if possible, be conducted using the same oxygen flow rate as was used in IMPALA and kept constant during the trial.

10.7.2. 6-Minute Walk Test (6MWT)

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

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

Data from both tests should be entered in the eCRF. Parameters to be recorded comprise pre and post walk dyspnoea score using the Borg (CR-10) Dyspnea Score (Appendix 4.1) SpO_2 (%) at start, worst SpO_2 (%) during the walk, distance walked (6MWD; m), duration of the walk (minutes and seconds), oxygen flow rate if applicable, reason for stop ping early (if applicable).

Trial specific instructions for the 6MWT are provided in Appendix 4.2.

If possible, the 6MWT should be conducted using room air. If a subject is on long-term oxygen therapy, oxygen should be given at their standard flow rate and held constant throughout the test. The tests conducted should be performed using the same oxygen conditions that were used in IMPALA, if possible.

10.7.3. Quality of Life Score (QoL)

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

Subjects will be asked to complete the SGRQ in the local language Appendix 4.3 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 the subject population of this trial.

10.7.4. Lung Function Tests

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

- DLCO (absolute value (measured), absolute value (predicted), % predicted, and haemoglobin)
- FEV_1 (absolute value and % predicted)
- FVC (absolute value and % predicted)

DLCO, FEV_1 and FVC will be assessed using local, appropriately calibrated equipment. Percent predicted values for FEV_1 and FVC will additionally be calculated centrally using standard equations.

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

The DLCO measurements should be performed in accordance ATS/ERS guidelines [Graham 2017]. Two acceptable tests should be conducted and the average of these will be calculated centrally. Based on same-day haemoglobin values, the haemoglobin corrected DLCO will be calculated centrally.

FEV_1 and FVC will be assessed using a local appropriately calibrated spirometer by site staff with documented training in lung function tests at the time points shown in Table 1. Measurements should be performed in accordance with ATS/ERS guidelines [Miller 2005].

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

10.7.5. 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 PaO_2 determined with the individual breathing room air in the supine position [Inoue 2006].

The DSS is a 5-point score as follows:

1 = no symptoms and $PaO_2 \geq 70$ mmHg

2 = symptomatic and $PaO_2 \geq 70$ mmHg

3 = 60 mmHg $\leq PaO_2 < 70$ mmHg

4 = 50 mmHg $\leq PaO_2 < 60$ mmHg

5 = $PaO_2 < 50$ mmHg.

If possible, the blood gas assessment should be conducted with the subject breathing room air (see Section 10.7.1). For subjects requiring supplemental oxygen during the blood gas assessment the DSS will be based on the PaO_2 obtained while breathing oxygen.

10.7.6. Overall Clinical Assessment

An overall clinical assessment will be done at the timepoints shown in Table 1. The status of aPAP will be categorised as: in remission, improving, stable, or progressive. The assessment will be based on investigator judgement.

The requirement for treatment will be categorised as: no treatment required, treatment with inhaled molgramostim required, or other treatment required.

If other treatment is required, such treatment should be recorded as described in Section 10.2.

10.7.7. Whole Lung Lavage

At each visit, information on whether WLL is required will be recorded. 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 WLL requirement will be documented.

Information about any WLL actually performed must be reported in the eCRF. The following information will be entered. Date of the WLL and type of WLL (unilateral, bilateral) will be recorded. Information about other assessments performed (e.g. blood gas measurements, lung function tests and exercise tests) before and after a WLL is performed should also be recorded.

10.8. Safety Assessments

The following safety variables will be assessed:

- AEs
- Physical examination
- Vital signs
- ECG
- Laboratory safety assessments
- CT scan, only if performed according to clinical standard

10.8.1. Adverse Events

Any AEs will be reported at every visit from Baseline (Visit 1) to the completion of the trial. 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 10.9.

10.8.2. Physical Examination

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

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

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

10.8.3. 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'.

10.8.4. Electrocardiogram (ECG)

A 12-lead ECG will be assessed using a standard ECG machine according to local procedures at the time points shown in Table 1. No central overreading will be performed.

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

10.8.5. Laboratory Assessments

The laboratory safety analyses (haematology and clinical chemistry) will be performed by local laboratories 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 4: Laboratory Safety Parameters

Category	Laboratory Parameter
Haematology	Haemoglobin, RBC, Red Blood Cell Distribution Width (RDW), Haematocrit, Mean cell volume (MCV), Mean cell haemoglobin (MCH), Mean cell haemoglobin concentration (MCHC), Platelet count, WBC and differential counts (absolute and percentage): Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Prothrombin Time International Normalised Ratio (PT-INR)

Category	Laboratory Parameter
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, C-Reactive Protein (CRP), and Glucose (non-fasting)

All results will be recorded in the eCRF and will be assessed as 'clinically significant' or 'not clinically significant'. Clinically significant findings identified at Baseline (Visit 1) should be recorded as medical history. Clinically significant findings not present at Baseline (Visit 1) should be reported as AEs.

10.8.5.1. PK assessment (Only for Italy)

The subjects enrolled in Italy will have Visits 1 - 6 scheduled for an on-treatment week during the allowed window of +/- 4 weeks. On the day of the visit, IMP dosing will be conducted at the site.

Two serum samples for analysis of GM-CSF will be collected at each of these visits. The first sample will be taken just prior to inhalation of molgramostim. The second sample will be taken 2 hours post dosing, (+/- 10 minutes). Samples will be shipped to a central laboratory for analysis. Further description of sample collection, processing, shipment and analyzing will be available in the laboratory manual. Timing of dose on the day before and on the day of sampling will be recorded in the eCRF.

10.8.5.2. Pregnancy Screen

A serum pregnancy test will be performed for female subjects of child-bearing potential at each visit. For subjects who have a gap between completion of IMPALA and Baseline (Visit 1), a urine pregnancy test will also be performed before dosing at Baseline (Visit 1) in order to immediately confirm that the subject is not pregnant. If treatment is not dispensed at Baseline (Visit 1), the urine pregnancy test will be performed at start of treatment. Female subjects of child-bearing potential will be instructed to conduct a monthly urine pregnancy test at home.

10.8.5.3. Computed Tomography (CT)

A CT scan is not required as part of this trial. Only if a CT scan is performed according to clinical practice or medical need, e.g. in case of a clinical deterioration, the results will be recorded in the eCRF as improved / worsened / no change / data missing – impossible to evaluate, compared to the last evaluation in IMPALA.

10.9. Adverse and Serious Adverse Events

10.9.1. Definitions of Adverse Events

10.9.1.1. Adverse Event (AE)

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

An AE can therefore be any 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.

10.9.1.2. Serious Adverse Event (SAE)

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 abnormality or birth defect
- May jeopardise the subject or may require medical intervention to prevent one or more of the outcomes listed above (Important Medical Events).

Life-threatening in the definition of an 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).

10.9.1.2.1. 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 trial.

10.9.2. Recording Adverse Events

All trial subjects will be carefully monitored for the occurrence of AEs during the trial period from Baseline to the last visit. The investigator will collect AEs using a non-leading question such as "have you experienced any new health problems or worsening of existing conditions" as well as reporting events directly observed or spontaneously volunteered by subjects.

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

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

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

10.9.2.1. 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.

10.9.2.2. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. Causality will be assessed as:

Probable

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

Possible

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

Unlikely

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

Not applicable

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

10.9.2.3. Outcome

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

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

10.9.2.4. 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.

10.9.2.5. 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.

10.9.3. Reporting Adverse Events

10.9.3.1. Serious Adverse Event (SAE) Reporting Procedure

The investigator is responsible for ensuring that all SAEs are reported to the sponsor immediately, using a trial-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 trial 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/IRB (if applicable) with any additional requested information (e.g. autopsy reports and terminal medical reports).

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

SAE REPORTING CONTACT DETAILS

Company: Premier Research

Department: Pharmacovigilance and Device Safety (PVDS)

E-mail: SavaraSafety@premier-research.com

Fax: +421 2 68203713

Note: If there is local legislation requiring investigators to report AEs to the Competent Authority or the IEC/IRB, the investigator should also comply with this legislation. If any such reporting is planned, this must be stated in the SAE report, and once the reporting has been performed, a copy of the reporting documentation must be enclosed with the SAE-Follow-Up 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 PVDS as soon as possible. SAE-Follow-Up reports also have to be recorded on the trial 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/her 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 IEC/IRBs concerned.

10.9.3.2. Suspected Unexpected Serious Adverse Reaction (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 IEC/IRB in all Member States concerned, to the European clinical trials database (Eudravigilance Clinical Trial Module - EVTCM), and if applicable, to other regulatory authorities according to local laws and regulations.

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

Any other SUSARs shall be reported to the Competent Authorities concerned and to the IEC/IRB concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

The investigator should be aware of local reporting regulations to the IEC/IRB. The Sponsor will either supply the investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB depending on local regulations.

10.9.3.3. Adverse Events of Special Interest

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

10.9.3.4. Precautions/Overdose

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

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

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

Haematologic findings such as leukocytosis 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.

10.9.3.5. Pregnancy

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

A pregnancy as such is not an AE, unless there is a possibility that the IMP has interfered with the efficiency of any contraceptive measures. However, the investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs, Section 10.9.3.1. The pregnancy report form should be used instead of the SAE form.

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

10.9.3.6. Safety Management Plan

The process of SAE-Assessment is performed by Premier Research. In this context a trial specific ‘Safety Management Plan’ has to be prepared before first subject is recruited into the trial. 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.

11. STATISTICS

No formal sample size calculation was done as this is an open-label extension trial. Up to 90 subjects will be included.

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 in tables and graphs. Individual subject data will be listed. Further details of all analyses will be given in the statistical analysis plan.

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

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

Interim cuts of data may be done on a yearly basis and as needed for regulatory purposes (e.g. 120-day safety update).

Data listings will show all recorded data.

Data from the trial is planned to be combined with relevant data from the IMPALA trial; these combined analyses will be reported separately.

11.1. Primary Endpoints

Number of AEs, SAEs, ADRs, and AEs leading to treatment discontinuation.

11.2. Secondary Endpoints

- (A-a)DO_2 during the trial
- 6MWD during the trial
- SGRQ total score during the trial
- Number of WLL and time to WLL during the trial.
- DLCO (% predicted), FEV_1 (% predicted), FVC (% predicted) during the trial
- PaO_2 and DSS during the trial
- Need for oxygen supplement therapy during the trial.
- Number of subjects not requiring treatment for aPAP and time off treatment after discontinuation of inhaled molgramostim.

11.3. Exploratory Endpoints

- GM-CSF levels before and 2 hours after dosing.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Access to Source Data and Documentation

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

12.2. Subject Records and Source Data

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

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

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

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

12.3. Study Monitoring

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

12.4. Audits and Inspections

Authorised representatives of Savara, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Savara audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements. The investigator should contact Savara immediately if contacted by a regulatory agency about an inspection.

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

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

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

13. ETHICS

13.1. Ethics Review

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

13.2. Ethical Conduct of the Study

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management

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

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

Changes to the data in the eCRF will be made at the site by delegated trial site personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the trial database. After database closure, the database will be exported as SAS® data sets.

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

14.1.1. Protocol Deviations

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

14.2. Inspection of Records

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

14.3. Retention of Records

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

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

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

15. FINANCE AND INSURANCE

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

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

16. TRIAL ORGANISATION

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

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

17. PUBLICATION POLICY

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

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

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

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

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

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

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

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19. APPENDICES

APPENDIX 1 LIST OF REVISIONS OF PROTOCOL

Table 5: Revisions of Protocol

Date	Version	Description of Document	Rationale for change
23-Oct-2017	1.0 This version was never submitted to any authorities	Final Protocol	NA
16-Nov-2017	2.0	Final Protocol, substantial amendment	NA
31-Jan-2018	3.0 This version only submitted in France and Denmark.	Substantial Amendment 1 to the protocol: The following updates have been made to the protocol: **Protocol synopsis**: • Detailed explanation of the possible treatment duration. **Flow chart:** • IMP will **not** be administered at visit 7, which is marked in the flowchart in protocol version 2. This is an error and will not be applicable in any country. **Section 10.8:** • It is clarified that CT scans only will be performed, if it is a part of clinical praxis. **Section 10.8.5.2:** • It is clarified that CT scan isn't a part of the protocol, and should only be performed as part of clinical praxis, e.g. clinical deterioration	• Elaboration of treatment duration requested by the authorities in France and Denmark. • Correction of an error. • Clarification required by the French authorities. • Clarification required by the French authorities.

Date	Version	Description of Document	Rationale for change
15-Mar-2018	Version 4.0 This version was only submitted in UK	Substantial amendment 2 to the protocol: The following updates have been made to the protocol: **Protocol synopsis:** Inclusion criterion 2: Clarification of inclusion criterion, including elaboration of sexual abstinence **Section 7.1** Inclusion criterion 2 Clarification of inclusion criterion, including elaboration of sexual abstinence	• Clarification to ensure full compliance with CTFG guidance 2014, which is a UK requirement but applicable for all countries • Clarification to ensure full compliance with CTFG guidance 2014, which is a UK requirement but applicable for all countries

	Version 5.0 Changes implemented for France and Denmark (Version 3.0) and UK (version 4.0) are made global in version 5.0 and applies to all countries in (version 5.0).	Substantial amendment 3 to the protocol: The following updates have been made to the protocol: **Protocol synopsis and flow chart:** The first sentence in the note to Inclusion criterion 2 is deleted. Exploratory endpoint added for GM-CSF levels before and 2 hours after dosing PK samples at visit 1-6 to be collected, only for patients in Italy. Note J is updated for patients in Italy: The visit should take place during the week on treatment and the dosing must be done at the clinic, in order to collect pre-dose PK. Clarification that spirometry and DLCO should be performed in accordance with European Respiratory Society/American Thoracic Society (ERS/ATS) guidance **Section 4.1:** The sentence "consistent with findings from other rhGM CSF products" deleted. For updates on MOL-PAP-002: The US added as a country and planned number of randomized patients increased from 90 to 135. Latest DSMB was in April 2018 and not October 2017, with 96 randomized patients. The last visit reviewed is changed from visit 12 to visit 13 and FU is now 48 weeks instead of 36 weeks. **Section 4.2** Rationale for collection of PK samples for Italian patients added. **Section 5.3.3**	• Guidance text inadvertently inserted. This is not relevant for molgramostim. • Sponsor decision in order to better characterize systemic safety • Missing in previous versions • Changes in the MOL-PAP-002 trial implemented and updates found relevant for the section • Sponsor decision in order to better characterize systemic safety • Sponsor decision in order to better

Date	Version	Description of Document	Rationale for change
		Exploratory endpoint added for GM-CSF levels before and 2 hours after dosing	characterize systemic safety
		Section 7.1 The first sentence in the note to Inclusion criterion 2 is deleted.	• Guidance text inadvertently inserted. This is not relevant for molgramostim.
		Section 9.5 A note for the Italy is inserted, to ensure the visits are scheduled in a week during treatment and the subject will administer the dose at the clinic, after collection of the pre-dose PK-sample.	• The note is added to ensure clarity in administration of IMP for the Italian subjects.
		Section 10.4.1: 6MWT instruction referral is added	• Missing in previous versions
		Section 10.4.7: Spirometry should be performed according to ARA/ERS guidelines.	• Missing in previous versions
		Section 10.7.2: Instructions for 6MWT is provided in Appendix 4.2 and not in a separate document.	• Missing in previous versions
		Section 10.8.5: All laboratory results must be entered in the eCRF.	• Sponsor decision in order to better characterize systemic safety
		Section 10.8.5.1: Additional PK samples requested to be collected for Italian patients.	• Sponsor decision in order to better characterize systemic safety
		Section 11.3: Exploratory endpoint inserted.	• Due to additional PK-sample collection
		Appendix 4.2: Instruction for 6MWT added.	• Missing in previous versions

APPENDIX 2 SIGNATURE PAGE

This Clinical Trial Protocol is approved by:

BIOSTATISTICIAN Date:
Simon Day, PhD Director Clinical Trials Consulting and Training Ltd
SPONSOR TRIAL DIRECTOR Date:
Mikkel Walmar, MSc, Pharm Manager, Clinical Operations Savara ApS **SPONSOR MEDICAL EXPERT** Date:
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APPENDIX 3 TRIAL ORGANISATION

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Clinical Research Organisation (Data Management and Biostatistics):

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APPENDIX 4 QUESTIONNAIRES

APPENDIX 4.1 BORG CR10 SCALE

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

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

APPENDIX 4.2 TRIAL SPECIFIC GUIDELINE FOR THE 6MWT

6 MWT AND CR10 (BORG'S) DYSPNOEA SCALE

6MWT

The 6MWT should be conducted according to ATS/ERS technical standard (Field Walking Tests in Chronic Respiratory Disease – Eue Respir J 2014; 44:1428-1446).

The 6MWT should be performed on a flat, straight course with a hard surface with little pedestrian traffic

The walking course should be 30 m or more in length.

The end of the course should be marked such that they are easily visible to patients. The same course should be used at each visit.

The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts

The test should be completed with the subject breathing room air, if possible. If a patient is on chronic oxygen therapy and not able to complete the 6MWT on room air, an oxygen titration procedure will be conducted at screening. The procedure described in Appendix 4 should be followed. The same flow of oxygen should then be used at the subject´s subsequent tests in the trial, unless a higher flow is required due to the subject's medical condition.

Patients should be encouraged every 60 seconds using standard phrases. Other words of encouragement and other nonverbal prompts should not be used.

If the patient stops walking during the test, the timer must not be stopped. The patient should be allowed to rest while sitting or standing, as they prefer. During the stop, standard encouragement should be given every 30 seconds. The time the patient stopped during the test, should be noted in the eCRF.

If SpO_2 is < 80% then the test should be stopped

Two 6MWTs should be performed (due to the learning effect on the test), and the result from the test with the longest distance walked should be recorded. If the subject is not able to complete more than one test due to exhaustion or adverse events, this should be noted on the worksheet. There must be at least 30 minutes between the two tests.

The total distance walked should be recorded

SpO_2 should be measured using a pulse oximeter continuously during the test. The start value and the lowest value during 6MWT should be recorded

Start heart rate and end heart rate should also be recorded

Use the study-specific worksheet for documenting values, which is provided by sponsor to the sites.

The results from the 6MWT with the longest distance walked and the related SpO_2 and CR10 (Borg) scale results should be entered in the eCRF.

Standard encouragement during a 6-minute walk test

1 min: You are doing well. You have 5 minutes to go.

2 min: Keep up the good work. You have 4 minutes to go.

3 min: You are doing well. You are halfway.

4 min: Keep up the good work. You have only 2 minutes left.

5 min: You are doing well. You have only 1 minute to go.

6 min: Please stop where you are.

If the patient stops during the test, every 30 s once SpO_2 is ≥85% the following standard phrase should be use:

"Please resume walking whenever you feel able."

CR10 Scale/Borg's dyspnoea scale

The CR10 (Borg's) scale for dyspnoea provided by Savara should be rated before and after the 6MWT. Let the patient read the instruction before rating their dyspnoea on the CR10 scale. Standard instructions for the CR10 (Borg scale) will be provided in local language.

If possible, the test should be conducted using the same oxygen flow level as was used in IMPALA. If a subject has started chronic oxygen therapy after being enrolled in IMPALA, an oxygen titration procedure should be conducted as described below.

This procedure only applies for patients on chronic oxygen supplementation at screening:

The patient will perform an O_2 titration procedure at Screening to determine the amount of supplemental oxygen that the patient needs to complete the 6MWT without developing O_2 desaturation. This oxygen flow rate will represent the patient's baseline O_2 flow rate for all subsequent 6MWT procedures for this study.

Equipment and supplies:

The equipment and supplies needed for the Oxygen Titration Procedure are the same as those needed for the 6MWT. Verify that your oxygen flow meter is accurate (to within 0.5 liters per minute).

Patient safety:

The safety precautions for the Oxygen titration procedure at the screening visit are same as required for the 6MWT.

Procedure:

Step 1: Resting O_2 Titration

Attach the pulse oximeter. Set it to alarm when SpO_2 falls below 83%.

Instruct the patient to sit still and not chat.

Discontinue supplemental oxygen. Start the timer for 10 min. If resting SpO_2 decreases to below 83% during the 10 minutes resting period, then start supplemental oxygen at 2 L/min. If resting SpO_2 again decreases below 83% during the next 10 minutes, then increase O_2 to 4 L/min. If resting SpO_2 remains below 83% during the next 10 minutes, then increase 0R2R to 6 L/min. If resting SpO_2 remains below 83% during the 10 minutes at rest on 6 L/min of supplemental oxygen, the patient should not conduct the 6MWT.

The lowest oxygen flow for which a patient can maintain a resting SpO_2 >83% for 10 minutes will be the initial flow rate for the Walking portion of the O_2 titration procedure.

Step 2: Walking O_2 Titration

Before starting the exercise evaluation, the patient should be seated and resting for at least 10 minutes on the oxygen flow rate determined during the resting O_2 titration procedure.

Follow the 6MWT procedures, starting at the O_2 flow rate established in the resting O_2 titration. Start the timer when the patient begins walking.

If the patient's SpO_2 decreases to below 83%, stop the walk and increase supplemental oxygen by 2 L/min. The patient should then be seated and allowed to rest for 5 min. The Walking O_2 titration procedure should then be repeated at the higher O_2 flow rate. If the patient's SpO_2 decreases to below 83% at any time, repeat the Walking titration. If during the 6MWT on 6 L/min of oxygen SpO_2 drops below 83% (sustained for at least 30 seconds), stop the walk. If the patient has not completed a distance of >150 meters, the patient should not conduct the 6MWT

The lowest oxygen flow on which a patient can complete the 6MWT without developing a SpO_2 below 83% will be the patient's O_2 flow for all subsequent 6MWT conducted during the course of the study.

APPENDIX 4.3 ST GEORGE'S RESPIRATORY QUESTIONNAIRE

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) one box for each question:

		most days a week	several days a week	a few days a month	only with chest infections	not at all
1.	Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2.	Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3.	Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4.	Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) one:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) one:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) one:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) one:

- No ☐
- Yes ☐

UK/ English (original) version 2

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St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

UK/ English (original) version 3

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St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

UK/ English (original) version 4

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St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

UK/ English (original) version 5

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St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

UK/ English (original) version 6

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