MOLGRAMOSTIM NEBULIZER SOLUTION

CLINICAL TRIAL PROTOCOL

SAV006-05

A randomized, double-blind, placebo-controlled clinical trial of once-daily inhaled molgramostim nebulizer solution in adult subjects with autoimmune pulmonary alveolar proteinosis (aPAP)

IMPALA-2

Product Name:	Molgramostim 300 µg nebulizer solution
Indication:	Autoimmune pulmonary alveolar proteinosis (aPAP)
Trial Phase:	3
IND:	126871
EudraCT:	2020-001263-85
EU Clinical Trial No:	2024-511052-41-00
Sponsor Name:	Savara ApS c/o Lundgrens Advokatpartnerselskab Tuborg Boulevard 12 DK-2900 Hellerup Denmark
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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A randomized, double-blind, placebo-controlled clinical trial of once-daily inhaled molgramostim nebulizer solution in adult subjects with autoimmune pulmonary alveolar proteinosis (aPAP).

Short Title

Once-daily inhaled molgramostim nebulizer solution in aPAP.

Rationale

Data from a completed phase 2/3 trial, MOL-PAP-002, suggested that molgramostim, an inhaled form of the recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), improves lung pathology, pathophysiology, and health status in subjects with aPAP in a dose-frequency dependent fashion. The present confirmatory phase 3 trial will be conducted to further investigate the efficacy and safety of molgramostim in subjects with aPAP.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
Investigate the efficacy of MOL compared to placebo	Primary
	• Change in % predicted DLCO from baseline to Week 24
	Secondary (For regulatory authorities outside of Japan and Korea)
	• Change in % predicted DLCO from baseline to Week 48 • Change in SGRQ Total from baseline to Week 24 • Change in SGRQ Activity from baseline to Week 24 • Change in EC (expressed as peak METs) from baseline to Week 24 • Change in SGRQ Total from baseline to Week 48 • Change in SGRQ Activity from baseline to Week 48 • Change in EC (expressed as peak METs) from baseline to Week 48 *Secondary (Specifically for Japan and South Korea)* • Change in SGRQ Total from baseline to Week 24 • *Change in SGRQ Activity from baseline to Week 24* • *Change in EC (expressed as peak METs) from baseline to Week 24* • *Change in A-aDO_2 from baseline to Week 24*

Objectives	Endpoints
	Exploratory • Frequency of WLL in the period between baseline and Week 24, and between baseline and Week 48 • Change in SGRQ Impact from baseline to Week 24 and Week 48 • Change in SGRQ Symptoms from baseline to Week 24 and Week 48 • Change in distance walked during treadmill test from baseline to Week 24 and Week 48 • Change in duration of exercise during treadmill test from baseline to Week 24 and Week 48 • Change in A-aDO_2 from baseline to Week 24 *(included as Secondary endpoint for Japan and South Korea)* and Week 48 • Change in PaO_2 from baseline to Week 24 and Week 48 • Change in DSS from baseline to Week 24 and Week 48 • Change in GGO from baseline to Week 24 • Change in CGIS from baseline to Week 24 and Week 48 • CGIC at Week 24 and Week 48 • Change in PGIS from baseline to Week 24 and Week 48 • PGIC at Week 24 and Week 48 • Change in supplemental oxygen use from baseline to Week 24 and Week 48 • Change in biomarker levels from baseline to Week 24 and Week 48 • Change in EQ-5D-5L from baseline to Week 24 and Week 48 • Change in dyspnea from baseline to Week 24 and Week 48 • Number of hospitalizations in the period between baseline and Week 24, and between baseline and Week 48 *Exploratory (Specifically for Japan and South Korea)* • *Change in % predicted DLCO from baseline to Week 48* • *Change in SGRQ Total from baseline to Week 48* • *Change in SGRQ Activity from baseline to Week 48* • *Change in EC (expressed as peak METs) from baseline to Week 48*

Objectives	Endpoints
Safety	
Investigate the safety of MOL compared to placebo	Safety Endpoints • Frequencies of (S)AEs, (S)ADRs, AESIs, deaths and AEs leading to withdrawal from trial and/or permanent discontinuation from treatment in the period between baseline and Week 24, and between baseline and Week 48 • Development of treatment-boosted anti-GM-CSF antibody titers during 24 weeks' treatment and during 48 weeks' treatment • Changes in FVC, FEV_1 and FEV_1/FVC from baseline to Week 24 and Week 48 • Change in QTcF from baseline to Weeks 4 and 24
Further Exploratory Longer-Term Objectives	
Investigate the efficacy of MOL during open-label treatment	Exploratory • Frequency of WLL in the period between baseline and the end of open-label treatment • Changes in % predicted DLCO, SGRQ Total, Activity, Impact and Symptoms, CGIS, PGIS, supplemental oxygen use, biomarker levels and EQ-5D-5L from baseline to the end of open-label treatment • Change in GGO from baseline to Week 144 and from Week 24 to Week 144 • CGIC and PGIC at the end of open-label treatment • Number of hospitalizations in the period between baseline and the end of open-label treatment
Investigate the safety of MOL during open-label treatment	Exploratory • Frequencies of (S)AEs, (S)ADRs, AESIs, deaths and AEs leading to withdrawal from trial and/or permanent discontinuation from treatment in the period between baseline and the end of open-label treatment • Development of treatment-boosted anti-GM-CSF antibody titers during double-blind and open-label treatment and 4 weeks' post-treatment • Changes in FVC, FEV_1 and FEV_1/FVC from baseline to the end of open-label treatment

Abbreviations: A-aDO_2=Alveolar-arterial oxygen difference; ADR=Adverse drug reaction; AE=Adverse event; AESI=Adverse event of special interest; CGIC=Clinician's global impression of change; CGIS=Clinician's global impression of severity; DLCO=Diffusing capacity of the lungs for carbon monoxide; DSS=Disease severity score; EC=Exercise capacity; FEV_1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; GGO=Ground glass opacity; GM-CSF=Granulocyte macrophage colony stimulating factor; METs=Metabolic equivalents;

MOL=Molgramostim 300 µg nebulizer solution; PaO_2=Partial pressure of oxygen; PGIC=Patient's Global Impression of Change; PGIS= Patient's Global Impression of Severity; QTcF=QT interval corrected by Fridericia; SADR=Serious adverse drug reaction; SAE=Serious adverse event; SGRQ=Saint George's Respiratory Questionnaire; WLL=Whole lung lavage.

Overall Design

- This is an interventional, randomized, double-blind, 2-arm, parallel, placebo-controlled, multi-center, phase 3 trial in adult subjects who are diagnosed with aPAP.
- 160 subjects with aPAP will be randomized and the randomization are intended to be stratified by baseline diffusing capacity of the lungs for carbon monoxide (DLCO; >50% or ≤50% predicted) and by region (Asia and Australia, Europe including Turkey, or North America).
- Autoimmune pulmonary alveolar proteinosis (aPAP) diagnosis should be confirmed by an anti-GM-CSF autoantibody test result, and history of PAP based on either high-resolution computed tomography, lung biopsy, or bronchoalveolar lavage cytology.
- The DLCO should be ≤70% predicted and the absolute change in % predicted DLCO should be <15% points during the screening period. The subject should have a stable resting oxygen saturation (SpO_2) >85% without use of supplemental oxygen.
- The trial consists of a 6-week screening period, a 48-week randomized, double-blind treatment period, a 96-week open-label treatment period, and a 4-week safety follow-up period. Taking the visit windows into account, the maximum treatment duration will be 145 weeks and the maximum trial duration will be 156 weeks.
- Two screening visits will be conducted at 6 and 3 weeks prior to the Baseline visit. At the Baseline visit, eligible subjects will be centrally randomized through an Interactive Response Technology system to 48-week double-blind once-daily treatment with either molgramostim 300 µg nebulizer solution (MOL) or placebo nebulizer solution (PBO). The treatment assignment will be stratified according to baseline % predicted DLCO and region.
- Subjects who complete the double-blind treatment period will continue into the open-label treatment period where they will receive open-label once-daily treatment with MOL.
- During the trial, whole lung lavage will be allowed as rescue treatment in case of worsening of aPAP.

Disclosure Statement

This is a parallel group treatment trial with 2 arms that is subject- and investigator-blinded.

Number of Subjects

With a total of 160 subjects, the power for showing an effect on change of percent predicted DLCO of 5.7 points with a standard deviation of 11 points is 90%.

The trial size will be re-evaluated by the Sponsor while remaining blinded to treatment after 80 patients have reached the 24-week primary endpoint time.

Intervention Groups and Duration

During the 48-week double-blind treatment period, subjects will be treated once daily with either MOL or PBO. All subjects who complete the double-blind treatment period will continue into the open-label treatment period where they will receive 96-week open-label once-daily treatment with MOL.

Statistical Analysis

The primary endpoint of change in % predicted DLCO will be analyzed with a general linear mixed model for repeated measurements, fitted with treatment, baseline % predicted DLCO, a binary indicator for DLCO stratification and a 3-level factor for region, and visit as categorical fixed effects, along with a treatment-by-visit interaction term. The estimated treatment effect will be the difference in least squares mean change in DLCO % predicted from baseline to Week 24, taken from the treatment-by-visit interaction term at 24 weeks. The estimated treatment effect will be presented with a 95% confidence interval and a P-value to test the null hypothesis that the effects of MOL and PBO are the same.

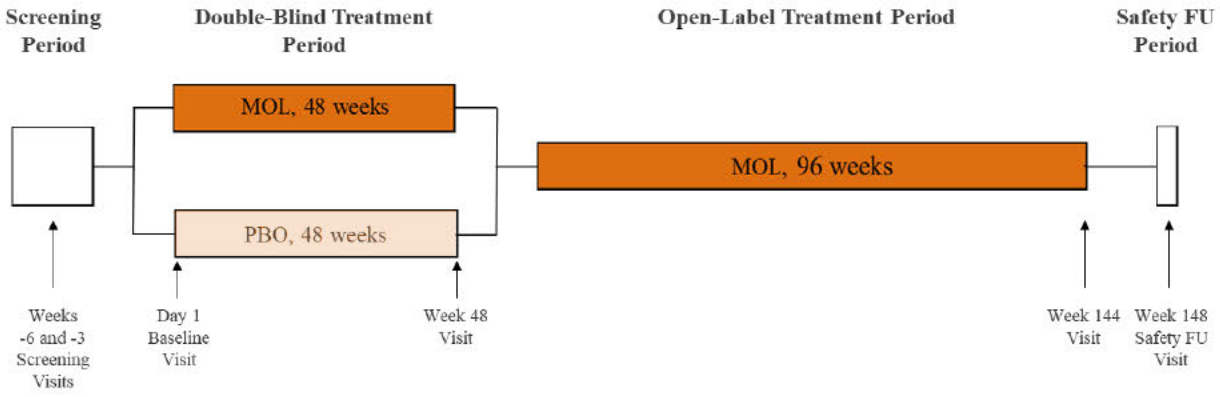
Any subject with missing % predicted DLCO data will have those missing values imputed using a multiple imputation method using a conservative control-based rule.

The seven secondary efficacy endpoints (change in % predicted DLCO from baseline to Week 48 and change in Saint George's Respiratory Questionnaire [SGRQ] Total, SGRQ Activity, and exercise capacity, from baseline to Week 24 and baseline to Week 48) will be analyzed the same way.

For Japan and South Korea only: There are four secondary efficacy endpoints (change in Saint George's Respiratory Questionnaire [SGRQ] Total, SGRQ Activity, and exercise capacity, from baseline to Week 24 and change in alveolar-arterial oxygen difference (A-aDO_2) from baseline to Week 24). All of these will be analyzed the same way.

Two Clinical Trial Reports (CTRs) will be prepared: the first CTR will include the results from the double-blind period up to Week 48 and a second CTR will include the results of the open-label period.

1.2. Schema



MOL = Molgramostim 300 µg nebulizer solution; PBO = Placebo nebulizer solution; FU = Follow-up

1.3. Schedule of Activities (SoA)

1.3.1. Double-blind Treatment Period

Visit Name	S1	S2	BL	W4	W8	W12	W16	W20	W24	W36	W48	Early withdrawal[a]	Unscheduled
Visit ID	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**EW**	**UN**
Visit window (days)	**± 7**	**± 7**	**-**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**NA**	**NA**
Weeks for Visit 3	**-6**	**-3**	**-**	**4**	**8**	**12**	**16**	**20**	**24**	**36**	**48**	**NA**	**NA**
Informed consent	X												
Medical history (including aPAP history)	X												
Prior and concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X												
Resting 12-lead ECG	X		X	X		X			X		X	X	(X)
Resting vital signs and body weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry and DLCO	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Physical examination	X	X[c]	X[c]	X	X[c]	X	X[c]	X[c]	X	X	X	X	(X)
Need for suppl. O_2 use or WLL	X	X	X	X	X	X	X	X	X	X	X	X	(X)
ABG sample and resting respiration rate			X			X			X		X	X[d]	(X)
Exercise treadmill test		X[d]				X[d]			X[d]		X[d]	X[d]	(X)
Handout of eDiary		X											
SGRQ[e]			X	X	X	X	X	X	X	X	X	X	(X)
PGIS & PGIC		X[f]	X[f]	X	X	X	X	X	X	X	X	X	(X)
EQ-5D-5L[e]			X			X			X		X	X	(X)
Oxygen diary[g]			X	X	X	X	X	X	X	X	X		
DSS			X			X			X		X	X	(X)
HRCT		X[d]							X[d]			(X[d])	(X)
CGIS & CGIC			X[h]	X	X	X	X	X	X	X	X	X	
Blood sample for diagnostic anti-GM-CSF autoantibodies	X												
Blood sample for pregnancy test and contraceptive check[i]	X	X	X[j]	X	X	X	X	X	X	X	X	X	(X)

Visit Name	S1	S2	BL	W4	W8	W12	W16	W20	W24	W36	W48	Early withdrawal[a]	Unscheduled
Visit ID	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**EW**	**UN**
Visit window (days)	**± 7**	**± 7**	**-**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**NA**	**NA**
Weeks for Visit 3	**-6**	**-3**	**-**	**4**	**8**	**12**	**16**	**20**	**24**	**36**	**48**	**NA**	**NA**
Samples for hematology, biochemistry and urinalysis	X	X[k]	X	X[l]	X[k]	X[l]	X[k]	X[k]	X	X[l]	X	X	(X)
Blood sample for biomarkers, anti-GM-CSF antibodies and, optionally, biobank[m]			X	X		X			X		X	X	(X)
Blood samples for GM-CSF, pre-dose and 2 hrs (±30 min) post-dose			X	X					X		X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility criteria[n]	X	X	X										
Randomization			X										
IMP administration training[o]			X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)
IMP dosing in clinic			X[p]	X	X	X	X	X	X	X	X[p]		
Dispense IMP and ancillaries			X	X	X	X	X	X	X	X	X		(X)
Return used and un-used IMP				X	X	X	X	X	X	X	X	X	
Return ancillaries												X	
Treatment compliance				X	X	X	X	X	X	X	X	X	(X)
Subject instruction and diary	X	X[q]	X[q]	X	X	X	X	X	X[r]	X[r]	X[r]	X	(X)
Exit interview									X[s]				

Abbreviations: ABG=Arterial blood gas; anti-GM-CSF=Anti-granulocyte macrophage colony stimulating factor antibodies; BL=Baseline visit; CGIC=Clinician's global impression of change; CGIS=Clinician's global impression of severity; DLCO=Diffusing capacity of the lungs for carbon monoxide; DSS=Disease severity score; ECG=Electrocardiogram; EQ-5D-5L=EuroQoL 5 Dimensions, 5 Levels; FU=Follow-up; GM-CSF= Granulocyte macrophage colony stimulating factor; hr=Hour; HRCT=High resolution-computed tomography; IMP=Investigational medicinal product; min=Minute; NA=Not applicable; PGIC=Patient's Global Impression of Change; PGIC= Patient's global impression of change; PGIS= Patient's global impression of severity; S1/S2=Screening Visit 1/2; SGRQ=Saint George's Respiratory Questionnaire; suppl. O_2=Supplementary oxygen; W=Week; WLL=Whole lung lavage; X=Mandatory procedure; (X)=Optional procedure to be performed if judged necessary by the Investigator.

a. The Early Withdrawal visit should be conducted if a subject is withdrawn from the trial before completion of the Week 48 visit. (See Section 1.3.2 for procedures to be conducted at the Early Withdrawal visit for the open-label treatment period.)
b. An unscheduled visit can be conducted if deemed necessary by the Investigator.
c. Symptom-oriented or brief physical examination as clinically indicated.
d. The exercise treadmill test and the HRCT scan can be performed up to 3 weeks after Screening Visit 2, but prior to the Baseline visit. At all other timepoints these assessments can be performed within 7 days after the scheduled visit. These

procedures, as well as ABG sample, should occur at the Early Withdrawal Visit only if the withdrawal occurs prior to Week 48.

e. SGRQ and EQ-5D-5L should be performed before any other trial procedures.
f. Only PGIS will be assessed at Screening Visit 2 and the Baseline visit. PGIS and PGIC should be completed immediately after the SGRQ and exercise treadmill test.
g. The oxygen diary should be completed daily, starting from 14 days prior to and until the visit (NB. Only applicable for subjects on supplemental oxygen).
h. Only CGIS will be assessed at the Baseline visit.
i. For visits with 12 weeks intervals (i.e., visits after Week 24), women of childbearing potential should also check pregnancy at home with monthly urine dipstick pregnancy tests.
j. A urine pregnancy test must also be performed at the Baseline visit, prior to first dosing.
k. Samples only include hematology at these visits.
l. Samples only include hematology and biochemistry at these visits.
m. Blood samples must be obtained before IMP dosing.
n. The eligibility criteria will be assessed to the extent they are available at Screening visits 1 and 2. At the Baseline visit, all eligibility criteria must be assessable and complied with for the subject to be randomized.
o. Re-training, marked as (X), can take place at all visits during the treatment period, if needed.
p. The subject will be observed for 1 hour after the first dose.
q. The Patient Journey sheet will also be handed out at Screening Visit 2 and collected at the Baseline visit.
r. Urine pregnancy test kits will also be provided to females of child-bearing potential.
s. Applicable for prospectively selected sites in North America and/or Europe. Can be performed up to 14 days after the Week 24 visit.

1.3.2. Open-label Treatment Period

Visit Name	W52[a]	W60	W72	W84	W96	W108 W120 W132 W144	W148 Safety FU[b]	Early withdrawal[c]	Unscheduled[d]
Visit ID	**V12**	**V13**	**V14**	**V15**	**V16**	**V17-20**	**V21**	**EW**	**UN**
Visit window (days)	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 14**	**± 7**	**NA**	**NA**
Prior and concomitant therapy	X	X	X	X	X	X	X	X	(X)
Resting 12-lead ECG			X		X	X		X	(X)
Resting vital signs and body weight		X	X	X	X	X	X	X	(X)
Spirometry and DLCO		X	X	X	X	X		X	(X)
Resting respiration rate			X		X			X	(X)
Physical examination		X[e]	X[e]	X[e]	X[e]	X[e]		X	(X)
Need for suppl. O_2 use or WLL		X	X	X	X	X		X	(X)
Return of eDiary						X[f]			
SGRQ[g]		X	X	X	X	X		X	(X)
PGIS & PGIC		X	X	X	X	X		X	(X)
EQ-5D-5L[g]			X		X	X		X	(X)
Oxygen diary[h]		X	X	X	X	X			
HRCT						X[o]			
CGIS & CGIC		X	X	X	X	X		X	
Blood sample for pregnancy test and contraceptive check[i]		X	X	X	X	X		X	(X)
Samples for hematology, biochemistry, and urinalysis		X[J]	X[j]	X[j]	X[j]	X[j]		X	(X)
Blood sample for biomarkers, anti-GM-CSF antibodies and, optionally, biobank[k]			X		X	X	X[b]	X	(X)
Adverse events	X	X	X	X	X	X	X	X	(X)
IMP administration training[l]		(X)	(X)	(X)	(X)	(X)[m]			(X)
IMP dosing in clinic		X	X	X	X	X[m]			
Dispense IMP and ancillaries		X	X	X	X	X[m]			(X)
Return used and un-used IMP		X	X	X	X	X		X	
Return ancillaries						X[f]		X	
Treatment compliance		X	X	X	X	X		X	(X)
Subject instruction and diary		X[n]	X[n]	X[n]	X[n]	X[m]		X	(X)

Abbreviations: anti-GM-CSF=Anti-granulocyte macrophage colony stimulating factor antibodies; CGIC=Clinician's global impression of change; CGIS=Clinician's global impression of severity; DLCO=Diffusing capacity of the lungs for carbon monoxide; DSS=Disease severity score; ECG=Electrocardiogram; EQ-5D-5L=EuroQoL 5 Dimensions, 5 Levels; FU=Follow-

up; GM-CSF=Granulocyte macrophage colony stimulating factor; HRCT=High resolution-computed tomography; IMP=Investigational medicinal product; NA=Not applicable; PGIC=Patient's Global Impression of Change; PGIC= Patient's global impression of change; PGIS= Patient's global impression of severity; SGRQ=Saint George's Respiratory Questionnaire; suppl. O_2=Supplementary oxygen; W=Week; WLL=Whole lung lavage; X=Mandatory procedure; (X)=Optional procedure to be performed if judged necessary by the Investigator.

a. The Week 52 visit is a safety telephone visit.
b. The Week 148 safety follow-up visit must be performed 3-5 weeks after the Week 144 visit. At the Week 148 visit, a blood sample for anti-GM-CSF antibodies will be obtained and any ongoing AEs at the Week 144 visit will be followed up.
c. The Early Withdrawal visit should be conducted if a subject is withdrawn from the trial before completion of the Week 144 visit. (See Section 1.3.2 for procedures to be conducted at the Early Withdrawal visit for the double-blind treatment period.)
d. An Unscheduled visit can be conducted if deemed necessary by the Investigator.
e. Symptom-oriented or brief physical examination as clinically indicated.
f. eDiary and ancillaries are to be returned at Week 144 only.
g. SGRQ and EQ-5D-5L should be performed before any other trial procedures.
h. The oxygen diary should be completed daily, starting from 14 days prior to and until the visit (NB. Only applicable for subjects on supplemental oxygen).
i. Women of childbearing potential should also check pregnancy at home with monthly urine dipstick pregnancy tests.
j. Samples only include hematology and biochemistry at these visits, except at Weeks 96 and 144 when urinalysis is to be performed as well.
k. Blood samples must be obtained before IMP dosing.
l. Re-training, marked as (X), can take place at all visits during the treatment period, if needed (NB. Does not apply at Week 144).
m. Does not apply at Week 144.
n. Urine pregnancy test kits will also be provided to females of child-bearing potential.
o. Subjects will undergo another HRCT scan only at the Week 144 visit.

2. INTRODUCTION

2.1. Trial Rationale

Molgramostim nebulizer solution is being developed by Savara for the treatment of autoimmune pulmonary alveolar proteinosis (aPAP).

Data from a completed phase 2/3 trial which was Savara's first trial in aPAP patients, MOL-PAP-002, suggested that molgramostim nebulizer solution improves lung pathology, pathophysiology, and health status in a dose-frequency dependent fashion (Section 2.2.3). Based on these findings, the present phase 3 trial will be conducted to further investigate the efficacy and safety of molgramostim nebulizer solution in aPAP.

2.2. Background

2.2.1. Autoimmune Pulmonary Alveolar Proteinosis (aPAP)

Pulmonary alveolar proteinosis (PAP) is a rare disease with an estimated prevalence in the United States (US) of 6.9 per 1,000,000 individuals (McCarthy et al. 2018). More than 90% of the reported cases of PAP are classified as autoimmune, whereas other variants (congenital and secondary PAP) account for less than 10% of cases. The prevalence of aPAP in Japan has been estimated to be 6.2 per 1,000,000 individuals (Inoue et al. 2008).

It has been shown that pulmonary granulocyte macrophage colony stimulating factor (GM-CSF) is required for terminal differentiation of alveolar macrophages (Shibata et al. 2001). Autoimmune PAP is mediated by autoantibodies targeting GM-CSF. Lack of GM-CSF leads to malfunctioning macrophages resulting in an impaired surfactant catabolism causing accumulation of surfactant in the alveoli which has a negative impact on the gas exchange between lung and blood (Trapnell et al. 2009).

PAP has a variable clinical course, ranging from spontaneous resolution to death from infections or progressive respiratory failure (Kumar et al. 2018). Most patients with aPAP present as adults in the third to fifth decade of life with exertional dyspnea of insidious onset with or without nonspecific respiratory symptoms (cough and/or production of white frothy sputum) or systemic symptoms (fatigue and/or weight loss), often lasting many months before evaluation or initial diagnosis. Fever and hemoptysis are less common and usually present only in the context of superimposed infection (Trapnell et al. 2019). In a large Japanese national PAP registry study, one-third of patients with aPAP were asymptomatic and were identified only through mandatory health screening programs (Inoue et al. 2008).

There are currently no approved pharmacological treatments for aPAP. Whole lung lavage (WLL) is the only treatment option available and is only performed in a limited number of specialized centers . The treatment goal in aPAP is to remove excess surfactant from the alveoli, improve gas exchange across the alveolar arterial barrier and reduce or eliminate long-term parenchymal lung damage. This is attempted with WLL, which is an invasive method to physically remove surfactant by 'washing' it out with saline. Although the procedure is reasonably well tolerated in most patients, it is associated with some morbidity from e.g.,

damage to the airways due to prolonged intubation, side-effects of general anesthesia and mechanical ventilation, and trauma to the alveoli from the washing procedure.

The invasive nature of and risks associated with WLLs, a limited access to centers that can perform WLLs, and the variable effect of WLLs due to lack of standardization emphasizes that there is an unmet need for a non-invasive, safe and well-tolerated, easily accessible and effective treatment for aPAP patients (Khan and Agarwal 2011).

2.2.2. Molgramostim Nebulizer Solution: Mode of Action

The active substance in molgramostim nebulizer solution, molgramostim, is a non-glycosylated form of recombinant human GM-CSF (rhGM-CSF), which is produced in a strain of *E. coli* bearing a genetically engineered plasmid which contains a human GM-CSF gene. Molgramostim is formulated in a sterile nebulizer solution which is supplied in vials containing 300 µg of molgramostim in 1.2 mL solution and is administered by inhalation via a nebulizer (eFlow Nebulizer System).

The rationale for investigating molgramostim nebulizer solution in respiratory diseases is based on the widely recognized ability of GM-CSF to promote differentiation and mobilization of different myeloid leukocyte subsets including neutrophils, tissue macrophages/dendritic cells or their circulating precursors. Along with other factors, GM-CSF also contributes to the proliferation of megakaryocytic and erythroid progenitors (Metcalf 1986; Park et al. 1986). Moreover, GM-CSF plays a key role in surfactant homeostasis, by maturation of alveolar macrophages (Hamilton 2008; Inaba et al. 1992; Bogunovic et al. 2009). It is crucially involved in anti-microbial pulmonary host defense (Unkel et al. 2012; Ballinger et al. 2006; Levine et al. 1999; Steinwede et al. 2011) and ameliorates lung injury when applied systemically to influenza virus-infected mice (Huang et al. 2011) by increasing size and activation of the alveolar macrophage pool. In addition to its effects on myeloid cells, GM-CSF was found to be crucial for alveolar epithelial repair following hyperoxic and inflammatory lung injury (Cakarova et al. 2009; Paine et al. 2003).

A detailed description of the chemistry, pharmacology, efficacy, and safety of molgramostim nebulizer solution is provided in the Investigator's brochure (IB).

2.2.3. Molgramostim Nebulizer Solution: Clinical Evidence

A phase 1 clinical trial with molgramostim nebulizer solution has been conducted in 42 healthy volunteers (MOL-001). In this trial, molgramostim nebulizer solution was well tolerated, no severe adverse events (AEs) or serious AEs (SAEs) were reported, and no dose-limiting toxicity was observed. Inhaled molgramostim was absorbed into the systemic circulation at levels approximately 50-100 times lower than have been shown after systemic administration of rhGM-CSF and induced the expected (i.e., in subjects without anti-GM-CSF antibodies) pharmacodynamic effects on white blood cell populations in a dose-dependent manner, i.e., increases from baseline levels in monocyte, eosinophil, and neutrophil counts. There was no development of anti-drug antibodies.

A randomized, double-blind, placebo-controlled, phase 2/3 trial in 138 adult subjects with aPAP has been conducted in 18 countries across Australia, Europe, Israel, Japan, Russia, South Korea, Turkey and the United States (MOL-PAP-002). Subjects received double-blind once-daily treatment for 24 weeks with either molgramostim 300 µg nebulizer solution continuous once-

daily treatment (MOL-OD; n=46), molgramostim 300 µg nebulizer solution in intermittent treatment cycles (MOL-INT; 7 days on and 7 days off treatment; n=45) or placebo nebulizer solution (PBO; n=47). After the double-blind period, there was a 24- to 48-week follow-up period, during which open-label treatment with alternating cycles of molgramostim nebulizer solution 300 µg daily for 7 days and no treatment for 7 days was provided to all subjects. In addition, in a European safety extension trial (SAV006-03), subjects from selected countries completing MOL-PAP-002 could roll over into long-term open-label treatment with alternating cycles of molgramostim nebulizer solution 300 µg daily for 7 days and no treatment for 7 days.

In MOL-PAP-002, the primary endpoint (the absolute change from baseline of the alveolar-arterial oxygen difference [A-aDO_2] after 24 weeks of treatment) improved (i.e., reduction in A-aDO_2) in all treatment groups. The estimated treatment differences versus PBO were −4.6 and −2.8 mmHg (least squares mean [LSmean]), for the MOL-OD and MOL-INT groups, respectively. These differences were not statistically significant. After unblinding and prespecified analyses, results were found to contain a non-physiologic (large negative) value for A-aDO_2 in one subject at Week 24. Re-examination of the data revealed this subject and 3 others (distributed across all treatment groups) had undergone blood gas analysis while breathing supplemental oxygen via nasal cannula, which precluded calculation of the true A-aDO_2 because the actual fraction of inspired oxygen (FiO_2) was unknown. The protocol had anticipated that some subjects would use supplemental oxygen during the test; to address for this confounding factor, the protocol required that these subjects used the same flow of supplemental oxygen at all testing time points and an estimated FiO_2 was included in the calculations based on standard conversion tables. In a post-hoc analysis with the 4 subjects who used supplemental oxygen removed, the estimated treatment differences versus PBO were −6.4 mmHg for the MOL-OD group (nominal p=0.0249) and −3.4 mmHg for the MOL-INT group (p>0.05).

As an alternative measure of gas exchange that is substantially less affected by use of supplemental oxygen, the diffusing capacity of the lungs for carbon monoxide (DLCO) was included as a secondary endpoint. The estimated differences versus PBO in LSmean change from baseline to Week 24 were 7.9% predicted for MOL-OD (nominal p=0.0074) and 2.9% predicted for MOL-INT (p>0.05). This pattern was supported by results for the post-hoc responder (>10% improvement in DLCO from baseline) analysis which showed odds ratios versus PBO of 3.14 (nominal p=0.0278) and 1.39 (p>0.05) for MOL-OD and MOL-INT groups, respectively.

Change in Saint George's Respiratory Questionnaire (SGRQ) Total score (the SGRQ includes questions related to three components [Activity, Impact and Symptoms] and the Total score is the sum of the scores of the component scores; Section 4.2.3.2 and Section 8.2.2) was a key secondary endpoint. The observed mean changes in SGRQ Total scores from baseline to Week 24 were larger for the MOL-OD and MOL-INT groups than for the PBO group (−12.3, −12.0 and −4.7 points, respectively). The estimated differences vs PBO in LSmean change from baseline to Week 24 were −7.6 for MOL-OD (nominal p=0.0103) and −7.0 for MOL-INT (nominal p=0.0173). This pattern was supported by results for the post-hoc responder analysis (≥4 units improvement) which showed odds ratios vs PBO of 3.78 for MOL-OD (nominal p=0.0075) and 2.78 for MOL-INT (nominal p=0.0307). The estimated differences in change from baseline to Week 24 were larger for the Activity and the Impact component scores (nominal p<0.05) than for the Symptoms component score (p>0.05).

For the second key secondary endpoint, 6-minute walk distance (6MWD), the observed mean changes in 6MWD from baseline to Week 24 were largest for the MOL-OD group, followed by the MOL-INT group and then the PBO group (39.6, 11.3, and 6.0 meters, respectively). The estimated differences vs PBO in LSmean change from baseline to Week 24 were 20.6 and 5.6 meters, respectively, for MOL-OD and MOL-INT (nominal $p>0.05$ for both comparisons). High baseline values for the 6MWD indicate a potential ceiling effect, and the variability for this endpoint was high despite efforts to standardize the testing across sites.

The third key secondary endpoint, time to need of WLL, was not different between the treatment groups. However, the number of WLL procedures required over the 24-week double-blind period was numerically in favor of MOL-OD and MOL-INT (9 and 7, respectively, compared to 17 for the PBO group). The yearly rate of WLL prior to the trial was 0.804 for all subjects, and in the double-blind period, rates were 0.422, 0.336, and 0.815 for MOL-OD, MOL-INT, and PBO, respectively. The rate ratios vs PBO using negative binomial regression were 0.284 for the MOL-OD group and 0.367 for the MOL-INT group ($p>0.05$). During the open-label follow-up period, a total of 5 WLLs were required, corresponding to a rate of 0.055 per subject year. Thus, the reduced rate of WLL compared with baseline and PBO in the double-blind period was sustained and reduced further during the follow-up period.

The subjects who had received PBO during the double-blind period showed improvements in the primary and key secondary endpoints in the follow-up period after switching to active treatment. Furthermore, the improvements observed in the active treatment groups during the double-blind period were maintained during the additional 24 to 48 weeks of open-label follow-up treatment.

In general, the profiles of treatment-emergent AEs, SAEs, adverse drug reactions (ADRs), severe AEs, and AEs leading to discontinuation were similar across the treatment groups during the double-blind period, and between the double-blind and follow-up periods. Only two AEs, Chest pain and Cough, occurred more frequently in the MOL-OD compared to the PBO treatment group.

Based on the positive findings noted above but acknowledging that the available data are not sufficient to demonstrate the substantial evidence of efficacy and safety required for regulatory approval, the present phase 3 trial will be conducted to further investigate the efficacy and safety of molgramostim nebulizer solution in aPAP.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

A summary of risks which may be associated with either the investigational medicinal product (IMP) molgramostim nebulizer solution or the trial procedures and mitigation strategies to address these is provided in Table 1. More detailed information about the risks associated with the IMP may be found in the IB.

Table 1: Summary of Risks and Mitigation Strategies

Investigational Medicinal Product (molgramostim nebulizer solution)	
Risk Title: Type I hypersensitivity reactions (including anaphylaxis, urticaria, angioedema and bronchoconstriction)	**Risk Description:** This is considered a risk due to the inherent risk of immunogenicity reactions to therapeutic proteins, although no hypersensitivity reactions were observed in clinical trials for molgramostim nebulizer solution.
	Risk Mitigation: First dosing will be conducted in the clinic. Subjects will be observed for any hypersensitivity reactions for 1 hour after the first dose. If a subject develops a type I hypersensitivity reaction further dosing should be suspended, permanently or temporarily, according to Investigator's judgment. The subject should be contacted by phone 8-12 hours after the event to check for any delayed reaction. Hypersensitivity reactions will be reported as AESIs with associated additional data collection to enable thorough evaluation in relation to regular monitoring activities during trial conduct. Subjects experiencing serious hypersensitivity reactions will be discontinued from the trial.
Risk Title: Use in Pregnancy	**Risk Description:** Embryo-fetal developmental toxicity studies in rabbits after subcutaneous dosing showed molgramostim-related embryo-fetal loss, and a slight increase in the incidence of major malformations at the highest dose level when dosed during early pregnancy. The safety factor based on AUC for plasma GM-CSF at NOAEL in rabbits and the theoretical AUC in aPAP subjects after inhalation of 300 µg dose is 19. The enhanced pre- and post-natal development study in cynomolgus monkeys following intravenous injection of molgramostim showed a higher frequency of abortions and early deliveries in molgramostim treated animals compared to control animals. A NOAEL could not be identified due to adverse findings at both dose levels. The AUC for plasma GM-CSF in cynomolgus monkeys at the lowest dose was 200-fold higher than the theoretical AUC in aPAP subjects after inhalation of 300 µg dose. Maternal health and post-natal survival and development of infants was unaffected by molgramostim treatment. No reports regarding the use of rhGM-CSF in pregnancy or lactation have been published. Studies in humans to determine effects of molgramostim nebulizer solution on fertility have not been undertaken.
	Risk Mitigation: Pregnant and breastfeeding women will not be included in this trial. Women of childbearing potential should use adequate contraception during the trial. Male subjects should agree to use condoms during the trial, or their female partner of child-bearing potential should use adequate contraception. During the trial check of contraceptive use and pregnancy testing will be performed in women of childbearing potential at each trial visit where molgramostim is dispensed. In addition, pregnancy testing will be performed at home at monthly intervals during treatment. If the patient becomes pregnant while receiving molgramostim nebulized solution, she should be apprised of the potential hazard to the fetus and treatment should be discontinued during pregnancy.

Risk Title: Cough	**Risk Description:** In MOL-PAP-002, there was a higher proportion of subjects reporting non-serious, mild to moderate Cough or Productive cough during 24 weeks' double-blind treatment in MOL-OD (~41%) compared to PBO (~30%). Onset of Cough did not appear to be linked to a certain duration of treatment. Duration of Cough varied from one day to ongoing.
	Risk Mitigation: Pulmonary function test will be performed as outlined in the Schedule of Activities and will, along with review of adverse events, be part of regular safety monitoring activities during trial conduct.
Risk Title: Chest pain	**Risk Description:** In MOL-PAP-002, there was a higher proportion of subjects reporting non-serious, mild 'Chest pain' cases during 24 weeks' double-blind treatment with MOL-OD (22%) compared to PBO (2%). Review of associated Reported terms as well as relevant co-occurring AEs did not indicate a cardiac origin of 'Chest pain', although two subjects in the MOL-OD group had 'Chest pain' without any co-occurring AEs or SAEs of non-cardiac origin, or any pre-existing cardiovascular medical history. As such it cannot be ruled out that these two 'Chest pains' may be of cardiac origin and/or result from MOL-OD treatment. Onset of 'Chest pain' did not appear to be linked to a certain duration of treatment. Duration of 'Chest pain' varied from one day to ongoing.
	Risk Mitigation: All subjects should be instructed to call the site if chest pain develops, and based on the information provided over the phone, additional investigations may be conducted according to Investigator's judgment. Chest pain will be reported as an AESI with associated additional data collection, including findings from any additional investigations conducted, to enable thorough evaluation in relation to regular safety monitoring activities during trial conduct.
Trial Procedures	
Risk Title: Blood sampling	**Risk Description:** Blood sampling is invasive and there is always a slight risk of bruising, infections, pain etc.
	Risk Mitigation: All blood sampling will be performed by trained staff and the volume of blood to be drawn at each occasion is small (10-40 mL)
Risk Title: DLCO	**Risk Description:** During the DLCO test, subjects will need to inspire minute amounts of carbon monoxide and tracer gases (e.g., 10% helium) and he/she needs to temporarily come off oxygen supply.
	Risk Mitigation: The DLCO is a well-known and frequently used test which will be performed on-site under supervision by qualified staff.
Risk Title: Exercise treadmill test	**Risk Description:** In subjects with preexisting heart and respiratory disease, e.g., angina, there may be a risk of exacerbation of these conditions during the test. The test must be performed without supplementary oxygen and this might induce a risk of desaturation. The assessment involves exercise on a treadmill which might cause a risk of fall.

	Risk Mitigation: The test will be performed in qualified laboratories under supervision by qualified staff. Contraindications for the test will be applied according to established clinical guidelines. The subjects will be monitored throughout the test including 12-lead ECG, HR, BP, SpO_2 and subjective symptoms. Termination criteria are applied in accordance with established clinical guidelines.
Risk Title: HRCT	**Risk Description:** Risk in connection with radiation.
	Risk Mitigation: The test is only mandated three times over the course of the study (i.e., over approximately 3 years), which should be consistent with routine HRCT frequency in this patient population.
Other	
Risk Title: Use of placebo	**Risk Description:** 50% of the subjects will be treated with placebo during the 48-week double-blind period. This might result in deterioration of aPAP.
	Risk Mitigation: Both active and placebo treatments will be added on top of current standard of care in form of supplemental oxygen when required and rescue treatment with WLL in case of worsening. Subjects who have been randomized to placebo and completed the first double-blind 48 weeks of the trial and have not permanently discontinued IMP due to unacceptable AE will be provided active treatment during the 96-week open-label treatment period.

Abbreviations: AE=Adverse event; AESI=Adverse event of special interest; aPAP= autoimmune pulmonary alveolar proteinosis; AUC=Area under the plasma concentration-time curve; BP=Blood pressure; DLCO=Diffusing capacity of the lungs for carbon monoxide; ECG=Electrocardiogram; GM-CSF=Granulocyte macrophage colony stimulating factor; HR=Heart rate; HRCT=High resolution-computed tomography; IMP=Investigational medicinal product; rhGM-CSF=Recombinant human granulocyte macrophage colony stimulating factor; MOL-OD=Molgramostim nebulizer solution once daily; NOAEL=No observed adverse effect level; PBO=Placebo; SpO_2=Oxygen saturation; WLL=Whole lung lavage.

2.3.2. Benefit Assessment

Currently, no approved pharmacological treatment nor any evidence-based treatment exists for aPAP. Due to the pathophysiology of aPAP, this condition can lead to associated morbidity, including respiratory infections, pulmonary fibrosis and potentially premature death. Thus, an unmet need for further treatment modalities exists. Successive WLL procedures remain the standard of care treatment with a symptomatic rather than a targeted pathophysiological approach.

Recent data from MOL-PAP-002 (Section 2.2.3) with a consistent numerical improvement on various endpoints, representing several elements of aPAP disease (i.e. lung pathology, pathophysiology, walking capacity, health status and need for rescue therapy) with no identified significant safety concerns indicate that molgramostim nebulizer solution may be a beneficial non-invasive and convenient treatment option for patients with aPAP.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risks to subjects participating in this trial, the risks associated with use of molgramostim nebulizer solution or the trial procedures are justified by the anticipated benefits that may be afforded to subjects with aPAP in this trial.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy	
Investigate the efficacy of MOL compared to placebo	Primary
	• Change in % predicted DLCO from baseline to Week 24
	Secondary (For regulatory authorities outside of Japan and Korea)
	• Change in % predicted DLCO from baseline to Week 48 • Change in SGRQ Total from baseline to Week 24 • Change in SGRQ Activity from baseline to Week 24 • Change in EC (expressed as peak METs) from baseline to Week 24 • Change in SGRQ Total from baseline to Week 48 • Change in SGRQ Activity from baseline to Week 48 • Change in EC (expressed as peak METs) from baseline to Week 48 *Secondary (Specifically for Japan and South Korea)* • Change in SGRQ Total from baseline to Week 24 • *Change in SGRQ Activity from baseline to Week 24* • *Change in EC (expressed as peak METs) from baseline to Week 24* • *Change in A-aDO_2 from baseline to Week 24* Exploratory • Frequency of WLL in the period between baseline and Week 24, and between baseline and Week 48 • Change in SGRQ Impact from baseline to Week 24 and Week 48 • Change in SGRQ Symptoms from baseline to Week 24 and Week 48 • Change in distance walked during treadmill test from baseline to Week 24 and Week 48 • Change in duration of exercise during treadmill test from baseline to Week 24 and Week 48 • Change in A-aDO_2 from baseline to Week 24 *(included as Secondary endpoint for Japan and South Korea)* and Week 48 • Change in PaO_2 from baseline to Week 24 and Week 48 • Change in DSS from baseline to Week 24 and Week 48 • Change in GGO from baseline to Week 24 • Change in CGIS from baseline to Week 24 and Week 48 • CGIC at Week 24 and Week 48 • Change in PGIS from baseline to Week 24 and Week 48 • PGIC at Week 24 and Week 48

Objectives	Endpoints
	• Change in supplemental oxygen use from baseline to Week 24 and Week 48 • Change in biomarker levels from baseline to Week 24 and Week 48 • Change in EQ-5D-5L from baseline to Week 24 and Week 48 • Change in dyspnea from baseline to Week 24 and Week 48 • Number of hospitalizations in the period between baseline and Week 24, and between baseline and Week 48 *Exploratory (Specifically for Japan and South Korea)* • *Change in % predicted DLCO from baseline to Week 48* • *Change in SGRQ Total from baseline to Week 48* • *Change in SGRQ Activity from baseline to Week 48* • *Change in EC (expressed as peak METs) from baseline to Week 48*
Safety	
Investigate the safety of MOL compared to placebo	Safety Endpoints • Frequencies of (S)AEs, (S)ADRs, AESIs, deaths and AEs leading to withdrawal from trial and/or permanent discontinuation from treatment in the period between baseline and Week 24, and between baseline and Week 48 • Development of treatment-boosted anti-GM-CSF antibody titers during 24 weeks' treatment and during 48 weeks' treatment • Changes in FVC, FEV_1 and FEV_1/FVC from baseline to Week 24 and Week 48 • Change in QTcF from baseline to Weeks 4 and 24
Further Exploratory Longer-Term Objectives	
Investigate the efficacy of MOL during open-label treatment	Exploratory • Frequency of WLL in the period between baseline and the end of open-label treatment • Changes in % predicted DLCO, SGRQ Total, Activity, Impact and Symptoms, CGIS, PGIS, supplemental oxygen use, biomarker levels and EQ-5D-5L from baseline to the end of open-label treatment • Change in GGO from baseline to Week 144 and from Week 24 to Week 144 • CGIC and PGIC at the end of open-label treatment • Number of hospitalizations in the period between baseline and the end of open-label treatment
Investigate the safety of MOL during open label treatment	Exploratory • Frequencies of (S)AEs, (S)ADRs, AESIs, deaths and AEs leading to withdrawal from trial and/or permanent discontinuation from treatment in the period between baseline and the end of open-label treatment

Objectives	Endpoints
	• Development of treatment-boosted anti-GM-CSF antibody titers during double-blind and open-label treatment and 4 weeks' post-treatment
	• Changes in FVC, FEV_1 and FEV_1/FVC from baseline to the end of open-label treatment

Abbreviations: A-aDO_2=Alveolar-arterial oxygen difference; ADR=Adverse drug reaction; AE=Adverse event; AESI=Adverse event of special interest; CGIC=Clinician's global impression of change; CGIS=Clinician's global impression of severity; DLCO=Diffusing capacity of the lungs for carbon monoxide; DSS=Disease severity score; EC=Exercise capacity; FEV1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; GGO=Ground glass opacity; GM-CSF=Granulocyte macrophage colony stimulating factor; METs=Metabolic equivalents; MOL=Molgramostim 300 µg nebulizer solution; PaO_2=Partial pressure of oxygen; PGIC=Patient's Global Impression of Change; PGIS= Patient's Global Impression of Severity; QTcF=QT interval corrected by Fridericia; SADR=Serious adverse drug reaction; SAE=Serious adverse event; SGRQ=Saint George's Respiratory Questionnaire; WLL=Whole lung lavage.

4. TRIAL DESIGN

4.1. Overall Design

- This is an interventional, randomized, double-blind, 2-arm, parallel, placebo-controlled, multi-center, phase 3 trial in adult subjects who are diagnosed with aPAP.
- The trial consists of a 6-week screening period, a 48-week randomized, double-blind treatment period, a 96-week open-label treatment period and a 4-week safety follow-up period (Section 1.2). The maximum treatment duration will be 145 weeks and the maximum trial duration will be 156 weeks taking the visit windows into account (Section 1.3).
- Two screening visits will be conducted at 6 and 3 weeks prior to the Baseline visit. It will not be possible to assess all eligibility criteria at the screening visits, but subjects should meet the eligibility criteria for which the relevant assessment results are available at one visit to proceed to the next visit.
- At the Baseline visit, it is mandatory to meet all eligibility criteria to proceed to randomization. Eligible subjects will be centrally assigned through an Interactive Response Technology (IRT) system to 48-week double-blind once-daily treatment with either molgramostim 300 µg nebulizer solution (MOL) or PBO. The treatment assignment will be stratified by region and baseline DLCO (Section 6.3).
- Subjects who complete the double-blind 48-week treatment period and who have not permanently discontinued IMP will continue into the open-label treatment period where they will receive once-daily open-label treatment with MOL.
- A safety follow-up visit (Week 148) will be conducted to follow-up on any AEs starting or ongoing at the end of open-label treatment (i.e., Week 144) and to obtain a 4-week post-treatment anti-GM CSF antibody sample.
- During the trial, WLL will be allowed as rescue treatment in case of worsening aPAP.
- Approximately 50-60 clinical sites will be involved, and each site is expected to randomize a minimum of 2 subjects.
- An independent data monitoring committee (DMC) will perform a safety evaluation during the trial (Section 9.7)

4.2. Scientific Rationale for Trial Design

4.2.1. Choice of Overall Trial Design

The randomized, double-blind, placebo-controlled, parallel-group trial design is a scientifically robust comparative design.

The use of a placebo arm controls for effects of the natural course of disease. The use of a placebo comparator arm is justified because there is no approved treatment that could be used as an active comparator in the present trial. Both active and placebo treatments will be added on top of current standard of care, in the form of supplemental oxygen when required and rescue treatment with WLL, in case of worsening. Furthermore, subjects who have been randomized to

placebo and completed the first 48 weeks of the trial will be provided active treatment for the additional 96 weeks.

The multi-center, international trial design allows for inclusion of subjects with aPAP from several regions of the world which will increase the generalizability of the results.

4.2.2. Choice of Subject Population

The subject population to be included in the current trial will be subjects with aPAP, which accounts for over 90% of PAP cases. Subjects with hereditary or secondary PAP will not be included. Hereditary PAP is often associated with a defect in the GM-CSF receptor so these subjects would be unlikely to benefit from rhGM-CSF treatment. In secondary PAP, treating the underlying cause of secondary PAP is usually sufficient to resolve the disease.

In addition, the aPAP condition should be associated with impaired DLCO, and impairment of exercise capacity (EC) demonstrated in the exercise treadmill test. Furthermore, DLCO must be stable during the screening period. These criteria should ensure randomization of subjects with stable moderate to severe disease and a potential for improvement. Subjects in need of rescue treatment (i.e., WLL) should have this procedure conducted prior to being screened for the trial.

It is expected that some subjects who have previously been treated with GM-CSF will be interested to participate in the trial. There is currently no evidence to indicate that previous treatment with GM-CSF would impact the response to a second treatment course. Therefore, subjects who were previously treated with GM-CSF (in a clinical trial, off-label, or through expanded access) may be randomized in the trial provided there is at least a 6-month wash-out prior to baseline, and they fulfill all eligibility criteria.

Subjects with hypoxemia in need of supplemental oxygen, either continuously, intermittently, or when required, may use this in accordance with clinical standards. However, certain trial assessments must be conducted with subjects breathing room air, and therefore subjects must be able to temporarily come off oxygen during trial visits without significant desaturation at rest. If the condition worsens during the trial so that they are not able to come off oxygen, these assessments will not be conducted due to the risk of obtaining inaccurate data. These assessments include the exercise test, which will, after an at least 15-minute oxygen saturation (SpO_2) stabilization period followed by a 5-minute monitoring period at rest, start conservatively at a very slow walking pace with no incline. The test will stop at specified termination criteria, including oxygen desaturation to 80% or lower (Section 8.2.3). Further, subjects must also be able to come off oxygen supply for a period of at least 15 minutes prior to conducting the DLCO maneuver. This interval provides an adequate margin to the specified minimum 10-minute period in the ATS/ERS guideline for DLCO (Graham et al. 2017). Lastly, prior to the arterial blood gas draw subjects must also be able to come off oxygen supply for at least 15 minutes, which was shown to be sufficient for 11 of 12 patients with chronic obstructive pulmonary disease (COPD) to stabilize after washing out supplemental oxygen (the 12th patient required 15.6 minutes) (Weinreich et al. 2013). Prior to all three assessments, oxygen saturation must be followed and should be confirmed to be stabilized prior to assessments, extending the 15-minute period if required.

4.2.3. Choice of Endpoints

4.2.3.1. Primary Endpoint

The primary endpoint is the change in % predicted DLCO from baseline to Week 24. The aim of this endpoint is to demonstrate treatment effect on gas exchange, using a standardized lung function test that has been shown to predict need for rescue treatment.

The DLCO is a clinically valuable test of lung function and was first described more than a century ago (Morrell 2015). It is based on the concept that the capacity for oxygen transfer from the alveolar gas to the pulmonary capillary blood can be estimated by measuring the passive diffusion of inhaled carbon monoxide. The single-breath technique of measuring the uptake of carbon monoxide in the lung is the most commonly used method globally. The DLCO test is convenient and the 10 seconds of breath-holding required for the DLCO maneuver is easy for most patients to perform.

The support for use of DLCO as a primary endpoint is based on the following findings:

- DLCO is a standardized measure of diffusing capacity, which is widely used in the clinical management of patients.

DLCO is widely used in the clinic to characterize the severity of gas exchange impairment in aPAP (Papiris et al. 2014; Tazawa et al. 2010; Wylam et al. 2006). As a pulmonary function test, DLCO is considered to better correlate with disease severity in aPAP than spirometry assessments (Bonella et al. 2011). It is performed in accordance with ATS/ERS guideline (Graham et al. 2017) , and further standardization across sites can be obtained by using the same equipment and implementing central overread.

- DLCO is a measure of the same pathophysiological process that results in the relevant clinical outcomes in aPAP.

The primary pathology of aPAP is a loss of pulmonary GM-CSF signaling that results in a defective alveolar macrophage function. This leads to the progressive accumulation of surfactant material in the lungs which physically impairs gas exchange across the alveolar membrane. Data from MOL-PAP-002 and published data (Tazawa et al. 2010) show a correlation between DLCO and the amount of surfactant accumulation, which supports this pathophysiological chain and, therefore, that DLCO is predictive of lung pathology assessed using an objective, physical sign of disease.

- DLCO predicts the major clinical event in aPAP, i.e., WLL.

Although there are no standardized, widely accepted criteria for WLL, there is general agreement among clinicians that lung function, computed tomography (CT) findings and subjective symptoms drive the decision to conduct a WLL. A published study from multiple clinical sites conducting WLL in adults found that 100% of sites used unspecified lung function decline (which would include DLCO) as an indication for WLL whereas 70% reported DLCO decline specifically as an indication (Campo et al. 2016).

A national retrospective study in Korea that included 78 PAP patients showed a statistically significant difference ($p<0.001$) in DLCO between patients who required treatment with WLL (57.5% predicted [SD 23.3]) and those who could be managed without WLL (82.3% predicted, [SD 20.7]) (Hwang et al. 2017).

Likewise, subjects requiring a WLL during the double-blind period of trial MOL-PAP-002 had a lower baseline DLCO than subjects who did not have a WLL. Summarizing baseline data for the two groups (excluding a single subject in the WLL group whose baseline DLCO was an extreme low outlier) resulted in 37.6% predicted (SD 11.3%) for subjects requiring a WLL versus 50.8% predicted (SD 15.5%) for those who did not. Looking at the DLCO at the visit just prior to conduct of WLL, the mean DLCO was 34.6% predicted (SD 12.6%) indicating that in most cases the WLL decision was related to a persistently low DLCO, rather than an acute worsening (which is also in line with the natural history of aPAP).

In conclusion, based on its properties as a standardized, widely used lung function test, directly relevant for the pathophysiology of aPAP, and predictive for the major clinical event of WLL, DLCO is considered suitable for use as the primary endpoint in this clinical trial for molgramostim nebulizer solution in aPAP.

4.2.3.2. Secondary Endpoints

The secondary endpoints SGRQ Total, SGRQ Activity, and EC, serve as clinically meaningful endpoints that address health status and function.

Saint George's Respiratory Questionnaire

The SGRQ is a questionnaire designed to measure health impairment in patients with asthma and COPD. It is also valid for use in bronchiectasis, has been used successfully in patients with kyphoscoliosis and sarcoidosis, and there is a report on validity in cystic fibrosis (Jones 2009).

Although SGRQ is not validated in aPAP, there are two studies in aPAP patients where SGRQ has been used, MOL-PAP-002 and a recently published study from China (Tian et al. 2020).

The SGRQ includes questions related to three components: Activity (activities that cause or are limited by breathlessness), Impact (social functioning and psychological disturbances resulting from airway disease), and Symptoms (effect of respiratory symptoms, their frequency and severity). A component score can be calculated for each component and a Total score can also be calculated that summarizes the impact of the disease on overall health status.

The Activity component assesses the patients' current state in terms of disturbance to patients' daily physical activity. The two questions used to calculate the Activity component score are disease non-specific and measure functional aspects of shortness of breath.

The baseline data from MOL-PAP-002 shows that a vast majority of patients are limited in their ability to walk up hills (94%), play sports (93%), and walk up a flight of stairs (81%). Patients are also commonly limited in their ability to walk around outside on level ground (46%), wash or dress themselves (37%), or walk around the house (28%). However, few patients report limitations while sitting or lying still (7%) or in taking a bath or shower (18%).

The concepts in the two questions that are used for the Activity component score assess activities that cause breathlessness or are limited by breathlessness. Breathlessness is a common symptom of aPAP. SGRQ Activity component thus seems to be a reasonable measure of breathlessness in aPAP patients.

The Impact component assesses the patients' current state, and measures impact of cough and breathlessness on a physical, psychosocial and daily activity perspective. The questions used to calculate the Impact component score are disease non-specific.

The baseline data from MOL-PAP-002 show that the most frequently reported impacts were getting exhausted easily from cough and breathlessness (67%), not feeling exercise is safe (62%) and not being able to play sports (80%).

The questions in the Symptoms component cover 4 symptoms (cough, sputum, shortness of breath, attacks of wheezing) and 4 additional symptom-related questions (number of severe or very unpleasant respiratory attacks, duration of worst respiratory attack, number of good days with few respiratory problems, and morning wheeze). The numbers of subjects who reported each of the 4 symptoms at baseline in MOL-PAP-002 are shown below (Table 2). Cough, sputum and/or shortness of breath (regardless of frequency) were present in a majority of subjects.

Table 2: Frequency of Symptoms in MOL-PAP-002 (% of Subjects)

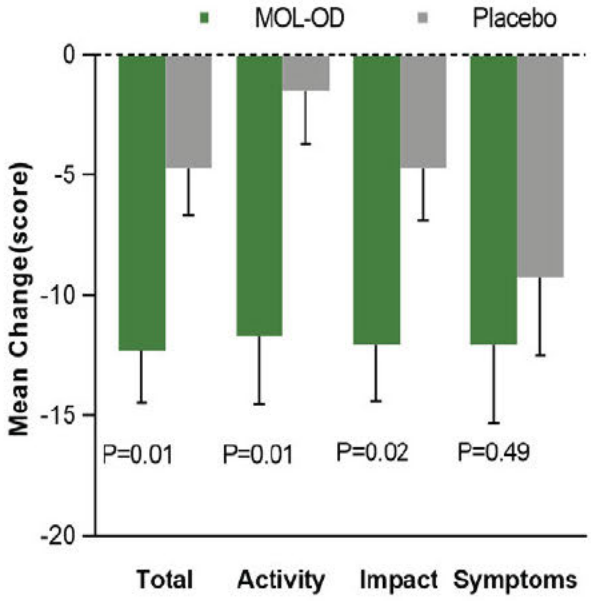
Symptom	Most days a week	Several days a week	A few days a month	Only with respiratory infections	Not at all
Cough	36	23	17	7	17
Sputum	32	18	16	5	29
Shortness of breath	42	16	23	5	14
Wheezing attacks	7	7	12	6	68

Based on published data, the symptom burden in PAP is available from three cohort studies: a Japanese cohort study involving 223 patients (Inoue et al. 2008), a German cohort study involving 70 patients (Bonella et al. 2011), and an Italian cohort study involving 73 patients (Campo et al. 2013). Dyspnea (shortness of breath) was most commonly reported, followed by cough. The data from MOL-PAP-002 is consistent with the literature of shortness of breath and cough being the major symptoms, reported by most subjects. Based on MOL-PAP-002 the frequency of sputum (elicited through direct questioning) seems to be higher than previously reported in the literature. Wheezing attacks is not a symptom that is thought to be associated with aPAP, as this is not an obstructive lung disorder. It is not clear why one third of subjects reported this symptom. In addition, almost 50% of the subjects reported respiratory attacks, and it is not clear what this concept covers in the context of aPAP.

Although not all symptoms included in the Symptoms component score are typically experienced by aPAP patients, the SGRQ Total score is a clinical endpoint that addresses direct patient benefit, i.e., overall respiratory health status including limitations in function from dyspnea.

In MOL-PAP-002, there was numerical improvement in the SGRQ Total score as well as component scores of MOL-OD over PBO, and there was nominal statistical significance for the Total score, the Activity component score and the Impact component score (Figure 1).

In particular, the Activity component score has high face validity in aPAP as it is focused on limitations in daily activities due to breathlessness. Likewise, the Impact component is not disease-specific and provides relevant data on the psychosocial impact of aPAP symptoms and activity limitations. By using the SGRQ Total score, both these components are covered, and a broad picture of patients' health status is provided.



Data represent observed means. Error bars represent standard error of mean (SEM).
MOL-OD = molgramostim 300 µg nebulizer solution once daily.

Figure 1: Change from Baseline to Week 24 in SGRQ Component Scores (MOL-PAP-002; MOL-OD and PBO Groups)

Thus, SGRQ Total and SGRQ Activity are considered appropriate for use as a clinically meaningful secondary endpoints in the present trial.

Exercise capacity

The main symptom in aPAP is exertional dyspnea, but dyspnea as a subjective symptom is difficult to assess in isolation, warranting parallel objective measures of performance during a structured bout of physical exertion (American Thoracic 1999; Johnson et al. 2010). EC as a functional measure of limitations related to dyspnea is a relevant, objective measure. In the present trial, the ability of inhaled molgramostim to improve alveolar-arterial oxygen transfer will be assessed. It is hypothesized that administration of molgramostim will improve EC as a greater amount of oxygen will be available to working skeletal muscle.

The US FDA has published a draft document in June 2019 entitled "*Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry*". In this document, EC is identified as a measure of function that is considered valuable for the purpose of approval of a drug.

The primary pathophysiology in patients with aPAP impairs a critical component of the oxygen transport pathway essential to the EC response, i.e., the alveolar gas exchange interface. Previous research in patients with pulmonary and heart disease have found DLCO to be correlated with EC (Elbehairy, O'Donnell, et al. 2019; Farkhooy et al. 2015; Elbehairy, O'Donnell, et al. 2019; Faggiano et al. 2001). Moreover, exertional dyspnea and oxygen desaturation with exercise are common symptoms in patients with aPAP (Inoue et al. 2008). As such, it should be of no surprise that EC has been found to be decreased in patients with aPAP (Bautin et al. 2005). Because the limitations in EC are related to the magnitude of pathophysiology in these patients,

exercise testing is recognized as an important component of disease severity assessment (Khan and Agarwal 2011) and guiding therapeutic decisions (Borie et al. 2011).

Given that exertional symptoms are hallmark characteristics in patients with aPAP and that profound limitations in EC were observed in a cohort of 7 patients with aPAP (Bautin et al. 2005), use of exercise testing as an endpoint in clinical trials in aPAP is warranted. Previous research supports this approach, indicating significant improvements in EC following WLL or subcutaneous GM-CSF in patients with aPAP (Beccaria et al. 2004; Schoch et al. 2002; Seymour et al. 2001).

The 6-minute walk test (6MWT) is an accepted method of assessing functional capacity in patients with pulmonary diseases (American Thoracic 2002; Holland et al. 2014). The MOL-PAP-002 trial assessed the 6MWD, which showed a trend to improvement with MOL-OD that did not reach statistical significance over PBO. The potential for improvement on this test in the overall trial population was limited by the relatively long distances, on average around 400 m, that subjects walked at baseline. For reference, in healthy persons, the mean 6MWD is reported as 580 m in men and 500 m in women (American Thoracic 2002). It is hypothesized that within the target population of moderate to severe aPAP, the test is not sufficiently sensitive in demonstrating improvements in function, because the test methodology does not force patients to achieve maximum EC. Furthermore, the variability of the test is large as it does not require subjects to exert maximum effort and thereby is highly dependent on subject motivation.

In the present trial, a ramp-up treadmill exercise test will be used to assess EC (Section 8.2.3). This is a well-accepted, reliable and valid (Fletcher et al. 2013; Arena et al. 2007; Puente-Maestu et al. 2016) approach to assessing baseline EC as well as changes in EC in an interventional trial. In fact, treadmill exercise testing overcomes several of the challenges associated with the assessment of EC through a timed walk test such as the 6MWT (e.g. ceiling effect, reliability, confounding effect of subject motivation/effort) (McLaughlin et al. 2009; Arena et al. 2007; Frost et al. 2005).

The main outcome of the exercise test is EC, expressed as peak metabolic equivalents (METs) achieved during the final stage a subject can perform. For each stage of the test, a MET value is defined based on a validated equation developed from the Fitness Registry and the Importance of Exercise National Database (FRIEND) registry. The FRIEND equation has been confirmed to significantly predict the peak measured oxygen consumption (VO_2; corresponding to peak MET) at a lower error rate compared to previously established equations (Kokkinos et al. 2017). Moreover, the difference between estimated and measured VO_2 has been shown to be greater for protocols with a large increment between stages (e.g. the modified Bruce protocol) compared to a conservative ramp test like the one proposed for this trial (Myers et al. 1991). In this context, the equation to calculate METs used in the current trial in conjunction with the conservative ramp protocol for exercise testing optimizes the accuracy in assessing EC in the current trial.

As previously noted, peak METs is a well-established and widely used measure of EC. In fact, the American Heart Association, which proposed EC be viewed as a vital sign (Ross et al. 2016), recognizes peak METs as an accepted expression of EC with high clinical value. The benefit of using peak METs as the key efficacy variable of the test is that it accounts for the increase in effort associated with the ramp-up of the test, where the effort required to complete the same distance in meters or duration in minutes will continuously increase. Thus, the METs required to achieve a fixed distance will increase over the course of the test. This makes it more

discriminatory for improvements in EC at the high end of the test. Furthermore, age- and sex-adjusted reference data are available in the literature (Kaminsky, Arena, and Myers 2015). Finally, there are well established published data on METs required to perform numerous daily activities and thus the achieved MET can be directly translated to the patient's capability to perform a specific activity (Ainsworth et al. 2011; Ainsworth et al. 2000; Jette, Sidney, and Blumchen 1990). However, distance walked and exercise duration will be included as exploratory endpoints.

In summary, a controlled exercise test that requires patients to reach their maximum EC by means of standardized increases in speed and grade on a treadmill is expected to be a good measure of function in this target population for the present trial.

Japan and South Korea only: Alveolar-arterial oxygen difference

For Japan and South Korea, A-aDO_2 will be used as an additional secondary endpoint as a measure of gas exchange. The absolute change from baseline of the A-aDO_2 after 24 weeks of treatment was the primary endpoint in MOL-PAP-002, and may therefore serve as a bridge from the results obtained in MOL-PAP-002 to the results obtained in the present trial.

4.3. Justification for Dose

In the present trial, treatment with molgramostim nebulizer solution 300 µg administered once daily in a double-blind fashion will be investigated against matching placebo for 48 weeks, and in an open-label fashion for a subsequent period of 96 weeks.

The recently completed MOL-PAP-002 trial confirmed that molgramostim nebulizer solution administered once daily over 24 weeks (i.e., MOL-OD) consistently showed a numerical improvement over the intermittent dosing arm with alternating weeks on and off treatment (i.e., MOL-INT). The MOL-OD regimen was nominally statistically significant over PBO for many of the secondary and exploratory endpoints in contrast to the MOL-INT regimen. The MOL-OD regimen is therefore proposed for further evaluation in the present clinical trial, considering that no important risks were identified with either of the investigated dose regimens.

As molgramostim nebulizer solution is intended for chronic treatment of patients with aPAP, a double-blind treatment period of 48 weeks is scheduled in the present trial to obtain efficacy and safety data during an extended period of time.

The subsequent 96-week period where all subjects will be given open-label treatment using the same dosing regimen will provide a possibility for active treatment to subjects who have been randomized to placebo during the first 48 weeks of the trial.

4.4. End of Trial Definition

A subject is considered to have completed the trial if he/she has completed the double-blind and the open-label treatment periods.

The end of the trial is defined as the date of the last visit on-site of the last subject in the trial.

5. TRIAL POPULATION

Subjects fulfilling all inclusion and none of the exclusion criteria can be randomized in the trial.

Prospective approval of protocol deviations to inclusion or exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Age

1. Subject must be ≥18 years of age, at the time of signing the informed consent. *Specific for Japan; Subject must be ≥20 years of age, at the time of signing the informed consent.*

Type of Subject and Disease Characteristics

2. A serum anti-GM-CSF autoantibody test result confirming autoimmune PAP.
3. History of PAP, based on examination of a lung biopsy, bronchoalveolar lavage (BAL) cytology, or a high-resolution computed tomogram (HRCT) of the chest.
4. DLCO 70% predicted or lower at the first screening and baseline visits.
5. Change in % predicted DLCO of <15% points during the screening period.
6. Willing and able to come off supplemental oxygen use prior to and during the treadmill exercise test, the DLCO assessment, and the arterial blood gas sampling.
7. Resting SpO_2 >85% during 15 minutes without use of supplemental oxygen at the screening visits.

Sex

8. Male or female
9. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    a. Male subjects: 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 below.
    b. Female subjects: Females who have been post-menopausal* for >1 year, or females of childbearing potential** after a confirmed menstrual period using a highly efficient method of contraception (i.e. a method with <1% failure rate such as combined hormonal contraception, progesterone-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence***), during and until 30 days after last dose of trial treatment. Females of childbearing potential must have a negative serum pregnancy test at the screening visits, and a negative urine pregnancy test at Baseline visit (Visit 3) and must not be lactating.
    * Post-menopausal is defined as no menses for at least 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not

using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
** A female is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
***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 trial 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.

Informed Consent

10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures specified in the protocol as judged by the Investigator.

5.2. Exclusion Criteria

Medical Conditions

1. Diagnosis of hereditary or secondary PAP, or a metabolic disorder of surfactant production.

Prior/Concomitant Therapy

2. WLL performed within 3 months prior to baseline.
3. Requirement for WLL at screening or baseline.
4. GM-CSF treatment within 6 months prior to baseline.
5. Treatment with rituximab within 6 months prior to baseline.
6. Treatment with plasmapheresis within 6 weeks prior to baseline.

Prior/Concurrent Clinical Trial Experience

7. Treatment with any investigational medicinal product within 5 half-lives or 3 months (whichever is longer) prior to baseline.
8. Previously randomized in this trial.

Other Exclusions

9. History of allergic reactions to GM-CSF or any of the excipients in the nebulizer solution.
10. Inflammatory or autoimmune disease of a severity that necessitates significant (e.g., more than 10 mg/day systemic prednisolone) immunosuppression.
11. Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product.

12. History of, or present, myeloproliferative disease or leukemia.
13. Apparent pre-existing concurrent pulmonary fibrosis, or diagnosis of interstitial lung disease other than aPAP.
14. Acute or unstable cardiac or pulmonary disease that may be aggravated by exercise or confound assessment of the primary endpoint: including presence of pulmonary edema, or diagnosis of chronic obstructive pulmonary disease (COPD), pulmonary vasculitis, or pulmonary hypertension.
15. Known active infection (viral, bacterial, fungal, or mycobacterial) that may affect the efficacy evaluation in the trial.
16. Physical disability or other condition that precludes safe and adequate exercise testing.
17. Any other serious medical condition which in the opinion of the Investigator would make the subject unsuitable for the trial.
18. Pregnant, planning to become pregnant during the trial, or breastfeeding woman. *For France only: including as further defined by French Health Code L-1121-5.*
19. *For France only: Any subject considered to be "vulnerable" on account of, e.g., mental or physical disability, socio-economic situation, or subjects deprived of their liberty, including as further defined by French Health Code articles L1121-6, L1121-8, and L1121-8-1.*

5.3. Lifestyle Considerations

Smoking is not allowed on the day of DLCO testing, prior to the test.

5.4. Screen Failures

Screen failures are defined as subjects who sign the ICF but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious AE (SAE).

In general, rescreening of subjects who do not meet the criteria for participation in this trial (screen failures) is not permitted. However, due to the rarity and natural course of aPAP, subjects may be rescreened in certain cases. Rescreening can only occur once and only after discussion with the Medical Monitor. The rescreened subjects should be assigned a new screening number and will need to perform all assessments again according to the SoA (Section 1.3). There will be a question in the electronic case report form (eCRF) to clarify whether the subject has been screened before.

6. TRIAL INTERVENTION

Trial intervention is defined as any IMP or medical device(s) intended to be administered to a trial subject according to the trial protocol.

6.1. Investigational Medicinal Products

6.1.1. Molgramostim and Placebo Dosing Regimen

Subjects will be randomized in a 1:1 ratio to MOL:PBO.

During the 48-week double-blind treatment period, subjects will be self-administering either MOL or PBO as a daily inhalation. All subjects who complete the double-blind 48-week treatment period and who have not permanently discontinued IMP will continue into the open-label treatment period where they will receive once-daily open-label treatment with MOL.

6.1.2. Packaging and Labelling

IMPs will be supplied in kits. Each individual kit will contain the necessary supplies to treat a subject for 1 week. Each time a new kit is used, a tear-off label should be placed in a Subject Instruction and Diary (Section 8.12) and the date of the first dose taken should be noted.

Packaging and labelling of the IMPs and the device used for administration (eFlow Nebulizer System) will be performed under the responsibility of the Sponsor in accordance with Good Manufacturing Practice and national regulatory requirements. Details about the packaging of the IMPs and the device is provided in Table 3.

Table 3: Investigational Medicinal Products in SAV006-05

Investigational Medicinal Product Name	Molgramostim 300 µg nebulizer solution (MOL)	Placebo nebulizer solution (PBO) Note: placebo nebulizer solution is matched to MOL in appearance, color and weight except for the active substance.
Active Substance	Molgramostim, recombinant human Granulocyte Macrophage Colony Stimulating Factor (rhGM-CSF)	Not applicable
Dose Formulation	Nebulizer solution	Nebulizer solution
Unit Dose Strengths	250 µg/mL	0 µg/mL
Dosage Levels	300 µg in 1.2 mL, daily	0 µg in 1.2 mL, daily
Device system used for administration	The eFlow Nebulizer System including controller, complete nebulizer handset and aerosol heads (single subject, reusable electronic nebulizer) and easycare (cleaning aid for aerosol heads) will be made available to all subjects.	The eFlow Nebulizer System including controller, complete nebulizer handset and aerosol heads (single subject, reusable electronic nebulizer) and easycare (cleaning aid for aerosol heads) will be made available to all subjects.

Route of Administration	Inhalation of MOL using eFlow Nebulizer System.	Inhalation of PBO using eFlow Nebulizer System.
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling (IMPs)	MOL: Provided in a kit containing 7 vials. Each kit will be labelled with a trial-specific label as required per local regulations and will be printed in local language. Device: The main components (controller and handset) of the eFlow Nebulizer System will be labelled with a trial-specific label and will be printed in local language. The easycare cleaning aid will be enclosed in the box with the controller). 0.9% saline (isotonic sodium chloride solution) needed for cleaning will be supplied.	PBO: Provided in a kit containing 7 vials. Each kit will be labelled with a trial-specific label as required per local regulations and will be printed in local language. Device: The main components (controller and handset) of the eFlow Nebulizer System will be labelled with a trial-specific label and will be printed in local language. The easycare cleaning aid will be enclosed in the box with the controller). 0.9% saline (isotonic sodium chloride solution) needed for cleaning will be supplied.

6.2. Dispensing/Administration/Storage/Accountability/Destruction

6.2.1. Dispensing

IMPs and ancillaries (e.g., nebulizer handsets) be dispensed at the trial visits summarized in SoA (Section 1.3). The IMP will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial.

On each dispensing occasion, an adequate number of kits and ancillaries will be dispensed to allow for the dosing regimen of once daily inhalation across the visit intervals (the intervals between each dispensing occasion are either 4 weeks or 12 weeks). A spare kit will be supplied to cover additional doses needed should visit scheduling require the ±7-day visit window. Additional kits can be assigned to subjects as required.

The IMP and device will be labelled with a unique identifier for dispensing and drug/device accountability.

IMP labels will comply with local regulations and will be printed in local language.

6.2.2. Administration

The eFlow Nebulizer System will be used to administer the IMP. This device has been specifically designed for use with molgramostim nebulizer solution. In the US, the device is designated as “Investigational” which is reflected on all labeling and accompanying documentation. This device is CE certified according to MDD 93/42/EEC.

The eFlow Nebulizer Handset 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 MOL or PBO, precisely defined droplet size and a high proportion of respirable droplets. The eFlow nebulizer handset will be replaced approximately every 4 weeks during the treatment period.

All subjects, investigators and trial nurses will be trained in IMP administration and medical device maintenance and assembling procedures. Training of the subject will take place at the Baseline visit prior to administration of the subject's first dose of IMP. The subject will administer the first dose of IMP at the Baseline visit (Visit 3) under the supervision of trial personnel. Training will ensure that critical tasks for the safe and efficacious delivery of the IMP using the eFlow Nebulizer System can be correctly completed. The subject's ability to perform a list of pre-specified critical tasks will be assessed and recorded on a worksheet that will be uploaded to the eCRF. A repeat assessment will be done at Week 4 (Visit 4). If re-training is needed at subsequent visits, the assessment will be repeated. The subject will be observed for any type I hypersensitivity reactions for 1 hour after the first dose.

Information on how to prepare the IMPs for administration will be provided in the 'eFlow Instruction for Use' and in the Subject Instruction and Diary.

During the treatment period, subjects will be instructed to always administer the trial treatment at approximately the same time of day. However, on days of trial visits, subjects will be asked not to take their trial treatment prior to the clinic visits. At each visit to the site, dosing will take place in the clinic, under supervision of trial staff and after all blood samples have been taken except the post-dose GM-CSF sample at selected visits. The time of dosing at site will be recorded. The subject should be instructed to take the last dose the day before the 48-week and 144-week visits.

In the event of a complaint related to the drug product or device, the subject should be instructed to immediately call the site. The site will complete a complaint form with all relevant details of the incident, including time, date, a description of the complaint and whether dosing was affected; refer to the Investigator Drug Manual, also known as the IMP Handling Manual or Pharmacy Manual, for the complaint form and instructions for completing and submitting the complaint form. For device-related cases, the eFlow Nebulizer System and/or nebulizer handset will be replaced, and the treatment should continue.

6.2.3. Storage

The IMPs should be stored at the trial site or at the site pharmacy as required by local regulations and laws for the participating sites. The Investigator will ensure that the IMPs will be stored in appropriate conditions in a secure location with controlled access. The storage compartment must be monitored, and the temperature documented. The IMPs must be stored at 2-8°C (35.6-46.4°F), must not be frozen or shaken and must be protected from sunlight and other light sources during storage. Any deviations in storage temperature must be reported to the Sponsor without delay as instructed in the Investigator Drug Manual. In case of a temperature deviation or damaged kit upon receipt or during storage at trial site, the affected IMPs must not be used until acceptance from the Sponsor. The Sponsor will decide if the affected IMPs may be released back into inventory, returned to the supply vendor, or destroyed locally. The affected IMPs

should be kept segregated in quarantine if evaluation results in the decision that the IMPs cannot be used.

Site staff should immediately document the kit status in IRT and contact their clinical research associate (CRA) for further guidance.

Storage of IMP and ancillaries at subjects' homes should be according to clinical labels and the Subject Instruction and Diary.

6.2.4. Accountability

The responsibility for the IMP and device is transferred from the Sponsor to the Investigator from the time of IMP and device receipt at the trial site to the time of destruction or return.

The Investigator is fully responsible for the IMPs at the trial site and for maintaining adequate control of the IMPs and eFlow Nebulizer Systems. The Investigator or delegated person should determine IMP kits and nebulizer handset accountability and complete the accountability logs. The IMP must be accounted for throughout the duration of the trial. Accountability of IMP is performed on a vial level and comments must be made in case of discrepancies. IMP accountability will be reviewed by the CRA 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.

6.2.5. Return and Destruction

Subjects are instructed to return all used/partly used and unused medication including empty packaging material at their next clinic visit and at the end of treatment visit. Compliance will be assessed at each visit by direct questioning and counting returned vials. This will be recorded in the source data (i.e., subject drug accountability form).

Unused and un-dispensed IMPs must be returned to the supply vendor on an ongoing basis or sent for local destruction after agreement with the Sponsor, but only after drug accountability has been completed and verified by the CRA. IMP return will be described further in the Investigator Drug Manual.

IMPs to be returned to the supply vendor can be stored at room temperature and must be stored separately from non-allocated IMPs. Returned IMPs should not be re-dispensed to the subjects.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Double-blind Treatment Period

All eligible subjects will be centrally randomized to IMP using an IRT system in the double-blind treatment period. The IRT system will ensure random allocation of eligible subjects to the MOL and PBO treatment groups.

The treatment randomization is intended to be stratified by baseline DLCO and by region. Thus, subjects will be randomized to treatment arms in a 1:1 ratio according to whether they have a DLCO of >50% predicted or ≤50% predicted. Furthermore, subjects will be regionally stratified

based on whether they are living in Asia and Australia, Europe including Turkey, or North America.

All subjects will inhale IMP once daily during the double-blind treatment period. Blinding will be ensured using a matching placebo.

A statistician otherwise not involved in the trial will prepare a computer-generated randomization list. The randomization list and treatment allocation list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and locked.

The IRT system will be integrated with the Electronic Data Capture (EDC) system and the log in information and instructions for the system will be provided to each site.

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

The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a subject's intervention assignment unless this could delay emergency treatment of the subject. If a subject's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

If code break is considered necessary for other safety concerns, for example due to signals of alerting ADRs and regulatory reporting of suspected unexpected serious adverse reactions (SUSARs), unblinding can be performed by the Sponsor without compromising blinded members of the trial team, and the reason for unblinding should be documented.

6.3.2. Open-label Treatment Period

All subjects who complete the double-blind 48-week treatment period and have not permanently discontinued IMP will continue into the open-label treatment period where they will receive once-daily open-label treatment with MOL.

6.4. Trial Intervention Compliance

Subjects' self-administration of IMP at home and treatment compliance will be assessed at each visit, including timing of dose (e.g., morning or evening). Compliance will be assessed by checking unused and used vials during the site visits and data will be entered in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of IMP vials dispensed to and taken by each subject must be maintained and reconciled with IMP and compliance records. Intervention start and stop dates, including dates for intervention delays, and compliance below 80% between the visits will also be recorded in the eCRF.

If a subject is found to be non-compliant, the Investigator should remind the subject of the importance of following the treatment instructions and the degree of and nature of non-compliance will be specified.

If a dose of IMP is missed, the subject should not adjust their dosing schedule to accommodate the missed administration. The subject should therefore not reschedule dosing to achieve the dosing regimen or add the missed dose to the next administration.

6.5. Prior/concomitant Therapy

6.5.1. Prior Therapy

Relevant prior therapy should be reported in the subject's medical record and the eCRF. Relevant prior therapy includes but is not necessarily limited to all previous WLL procedures, plasmapheresis procedures, GM-CSF, rituximab, statins and pioglitazone treatment (life-long recall period). Use of supplemental oxygen or any other treatment for aPAP should be reported for a period of 6 months prior to Screening Visit 1. All other prior therapy should be reported if considered relevant by the Investigator.

6.5.2. Concomitant Therapy

The use of concomitant medicines or other treatment regimen during the trial should be kept at a minimum and as stable as possible.

During the trial, subjects must abstain from the therapies described in Table 4.

Table 4: Disallowed Therapy

Therapy
Any GM-CSF other than the IMP
Rituximab
Plasmapheresis
Any investigational medicinal product (this also includes approved products when administered as experimental therapy for aPAP)

The disallowance of these therapies should start at the time of signing informed consent. Subjects who want to start disallowed therapy for aPAP must withdraw from the trial and will not be able to re-enter, e.g., in the open-label period.

Any therapy that the subject is receiving at the time of screening or receives during the trial must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, dose unit and frequency
- Administration route

6.5.3. Rescue Treatment

During the trial, WLL is allowed as rescue treatment for worsening aPAP.

Subjects in need of WLL prior to the trial should have the procedure performed at least 3 months before Baseline, and therefore screening activities cannot be started until approximately 6 weeks after the WLL. Subjects who require a WLL during screening or at baseline are not eligible. Such subjects may be rescreened once, after consultation with the Sponsor and respecting the window for pre-trial WLL so that fulfilment of the inclusion criteria can be established after the WLL.

The primary reason for conducting WLL should be provided in the eCRF. Date of the WLL and type of WLL (right or left lung), amount of saline used, and time used for performing the WLL will be documented. For sites applying therapeutic segmental or lobar lavages, such lavages will also be recorded.

Before and after WLL, an assessment of DLCO, and other relevant assessments according to the Investigator's discretion, should be obtained. This could be done at the regular trial visits, provided that they occur within 4 weeks prior to and after the procedure, respectively. Otherwise, an unscheduled visit should be conducted. If two unilateral WLLs are conducted in a preplanned sequence less than 4 weeks apart, the DLCO assessments should be done within 4 weeks before the first WLL and after the second WLL, respectively.

6.5.4. Oxygen Supplementation

Oxygen supplementation may be considered necessary for subject safety and well-being and may be given according to clinical standards at the discretion of the Investigator. Indications for oxygen supplementation will be recorded in the eCRF by the Investigator or designee and subjects will self-report actual oxygen use during the trial.

However, certain trial assessments (i.e., the exercise treadmill test, DLCO test and arterial blood gas assessment) must be conducted with subjects breathing room air, and therefore they must be able to temporarily come off oxygen during trial visits without significant desaturation at rest (see Section 4.2.2).

If a subject is unable to come off supplemental oxygen prior to any of these trial assessments, the assessment will not be performed. The reason for omitting an assessment should be documented in the eCRF. The subject will continue in the trial and conduct all other assessments according to the protocol.

6.6. Dose Modification

The dose of the IMPs must not be modified in the trial.

6.7. Intervention after the End of the Trial

After completion of the trial, the Investigator will advise trial subjects on access to appropriate and available treatment options.

7. DISCONTINUATION OF TRIAL INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Investigational Medicinal Product

In rare instances, it may be necessary for a subject to discontinue IMP, if deemed necessary by the Investigator.

Potential reasons for discontinuation of IMP are:

- Lack of efficacy/worsening of disease
- Unacceptable AE (Section 8.4.3)
- Pregnancy (Section 8.4.5)

If IMP is discontinued, the subject will remain in the trial and will be encouraged to continue to follow the same visit schedule, i.e., they will continue through the 48-week double-blind period and then they may continue into the open-label period.

The reason and date the subject is discontinued from IMP will be documented in the eCRF.

7.2. Withdrawal from the Trial

A subject may withdraw from the trial at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. Withdrawal from the trial will not affect or prejudice the subject's further care or treatment.

At the time of withdrawal from the trial, if possible, an early withdrawal visit should be conducted, as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of trial withdrawal and follow-up and for any further evaluations that need to be completed. The reason and date the subject is withdrawn from the trial will be documented in the eCRF.

Subjects who withdraw before randomization will be considered screen failures.

If a subject withdraws from the trial, the data collected on the subject to the point of withdrawal (including data and samples collected during the early withdrawal visit, if conducted) remain part of the trial database and will not be removed.

If a subject withdraws from the trial and withdraws consent for analysis of samples taken but not yet analyzed, the Investigator or designee must document this in the site trial records and expedite notification to the Sponsor. The Sponsor will notify the relevant laboratories and request destruction of any stored biological material in accordance with the subject's wishes.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the clinic for a required trial visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial.

Discontinuation of specific sites or of the trial as a whole is described in Section 10.1.

8. TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the SoA (Section 1.3). The informed consent process must be completed prior to any other assessment or procedure.

At each visit, where applicable, the order of assessments should preferably follow the order in the SoA. However, the following sequences must be adhered to:

- Assessments in the eDiary (SGRQ, immediately followed by the corresponding SGRQ-related PGIS and, where applicable, PGIC; and EQ-5D-5L) should be done before any other assessments.
- For the pulmonary function tests, spirometry assessment should be performed prior to the DLCO assessments.
- Arterial blood gas sampling and other laboratory sampling must be done prior to IMP dosing at site.
- At visits, where the exercise treadmill test is conducted, it may be done on a separate day than the other assessments. If the exercise treadmill test is done on the same day, it should be done after pulmonary function tests and arterial blood sampling. The corresponding exercise-related PGIS and, where applicable, PGIC, should be done immediately after the exercise treadmill test.
- AE assessment should be done after IMP dosing at site.

Protocol waivers or exemptions are not allowed.

Safety concerns may lead to discontinuation of IMP if deemed necessary by the investigator.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

At the Baseline visit, all screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

8.1. Demographics and Medical History

8.1.1. Demographics

The following demographics of each subject will be collected at Screening Visit 1:

- Year of birth
- Weight (kg) in indoor clothes without shoes
- Height (cm) without shoes
- Sex
- Race (White/Asian/Black/American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander)

- Smoking (Previous/Current/Never; Start year/Average number of packs per day for previous and current smokers, and additionally Stop year for previous smokers)
- Occupational dust exposure (Previous/Current and Type/Start year and, if applicable, Stop year, of exposure)

8.1.2. Medical History and History of aPAP

Relevant medical history of each subject, including all current diseases, and relevant prior diseases, including recent respiratory infections, will be recorded at Screening Visit 1.

In addition, the following aPAP history information will be collected at Screening Visit 1 in a separate eCRF module:

- Date of PAP diagnosis plus information regarding evidence of PAP (HRCT, biopsy or BAL cytology according to inclusion criterion no 3)
- Date of first positive anti-GM-CSF antibody test
- Information about previous WLL and plasmapheresis procedures, GM-CSF treatment and use of supplemental oxygen

8.2. Efficacy Assessments

8.2.1. Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)

As a measure of pulmonary gas exchange, a standardized lung function test, DLCO, will be conducted at the timepoints shown in the SoA (Section 1.3). See also Section 4.2.3.1 for further information regarding DLCO.

The single-breath DLCO test will be performed in accordance with ATS/ERS guidelines for DLCO testing (Graham et al. 2017), and further standardization across sites will be obtained by using standardized equipment (EasyOne Pro®, ndd Medical Technologies) and implementing central overread by a team of external, independent respiratory experts. A manual will be provided to all trial sites that will describe the procedure for DLCO testing in more detail.

In order to avoid impact on the DLCO by an acute respiratory infection, subjects experiencing such infection should be asked to contact the site and the visit should be postponed, if possible, within the visit window. If a subject attends the visit anyway with an acute respiratory infection, this should be noted in the eCRF, either as concurrent disease (if detected or diagnosed prior to signing of ICF at Screening Visit 1) or as an AE (all other timepoints).

Subjects must be asked to refrain from smoking on the day of the test. If the subject is a regular smoker, the date and time of the last cigarette smoked prior to the DLCO must be recorded.

All subjects should be seated for at least 15 minutes prior to the DLCO testing. Subjects on supplemental oxygen should discontinue their oxygen supply at the start of this 15-minute resting period. During this period, oxygen saturation is monitored and recorded every 5 minutes and must be stable prior to initiating the DLCO maneuver. Oxygen saturation stability is defined as a change of ≤2 % points over 5 minutes. If the stability criterion is not met after 15 minutes, the resting period should be prolonged with 5 minutes at a time, until stability is confirmed. Subjects who need to administer oxygen between maneuvers should go through the same

stabilization procedure prior to the next maneuver. If a subject does not tolerate discontinuation of oxygen until stabilization, the DLCO assessment will not be conducted. The reason for missing data must be recorded.

The predicted DLCO value will be calculated by the centrally provided equipment according to the Global Lung Function Initiative prediction equation (Stanojevic et al. 2017).

The measured DLCO value will be adjusted for the hemoglobin (Hb) value obtained from the central laboratory, expressed in g/dL, using the following formula:

- Males: Predicted DLCO adjusted for Hb = Predicted DLCO / (1.7Hb/(10.22+Hb))
- Females: Predicted DLCO adjusted for Hb = Predicted DLCO / (1.7Hb/(9.38+Hb))

For each subject, an adjusted value of % predicted DLCO will be derived based on the adjusted absolute value.

The Hb value from the same day as the DLCO test will be entered into the DLCO device when available from the central laboratory to be used for adjustment. For decision on inclusion / exclusion at baseline, the Hb value obtained at Screening Visit 2 will be used for real time adjustment of % predicted DLCO results at the Baseline visit. For analysis of the trial data, the % predicted DLCO results at baseline will be adjusted for Hb based on the Hb value obtained at the Baseline visit.

At least two acceptable and repeatable maneuvers according to ATS/ERS criteria are required. Up to five maneuvers may be conducted, if needed, during a session. For the final DLCO result the average of the two best efforts, as determined by the overreader, will be used. Central overread will be conducted real time (within 1 hour) at baseline, Week 24 and Week 48. Only results from the overread may be used for determining eligibility criteria for the trial.

8.2.2. Saint George's Respiratory Questionnaire (SGRQ)

As a measure of respiratory health impairment, including limitations in activity due to breathlessness and psychosocial impact of respiratory problems, SGRQ will be used at the timepoints shown in the SoA (Section 1.3).

The SGRQ (Section 10.2.1) includes questions related to three components: Activity (activities that cause or are limited by breathlessness), Impact (social functioning and psychological disturbances resulting from airway disease), and Symptoms (respiratory symptoms, their frequency and severity). The questionnaire has a recall period of 4 weeks for Symptoms, whereas Activity and Impact components address the subject's current state.

See also Section 4.2.3.2 for further information regarding SGRQ.

Subject must complete the SGRQ on their own in the eDiary, before any other trial procedures are performed, but someone from the trial staff should be available to give advice if required.

As an additional global measure of health, the subjects will be asked to grade their current health on a 5-point scale (very poor, poor, fair, good, or very good). This question is included within the SGRQ questionnaire; however, the question is not included in the calculation of the SGRQ scores.

After completion of the SGRQ, the PGIS and PGIC (at post-baseline visits) will be completed (see Section 8.2.12).

8.2.3. Exercise Capacity (EC)

As a functional measure of exertional limitations related to dyspnea, EC will be assessed by an exercise treadmill test at the timepoints shown in the SoA (Section 1.3). See also Section 4.2.3.2 for further information regarding EC assessment and the treadmill test. EC will be expressed in peak METs (1 MET=3.5 mL O_2/kg/min).

A conservative ramp-up treadmill protocol, employing minimal adjustments in speed and grade from one stage to the next, will be used. The highest treadmill speed and grade achieved will be used to calculate peak METs. The treadmill test will be conducted at local exercise testing laboratories by qualified staff experienced in the conduct of clinical exercise testing.

Standardization across the exercise testing laboratories will be obtained by generating a trial-specific Exercise Test Manual that follows established guidelines (Myers et al. 2009; Myers et al. 2014) and by implementing central overread by an external, independent expert (exercise test core laboratory). The overreader will review all data collected in the test, require clarification of questionable data, and make the final confirmation that the exercise test is valid (i.e., maximal EC achieved) according to the pre-specified criteria.

Subject instructions on the needed preparations before the test will be provided to the subject in the Subject Instruction and Diary (e.g., meal composition and timing before the exercise test, what type of clothes to wear, etc.) (Section 8.12). When the subject arrives to the exercise testing laboratory, she/he will receive detailed information on:

- How the exercise test will be conducted, with emphasis on the use of a conservative ramp-up protocol (i.e., treadmill starts very slowly at no gradient).
- Monitoring (i.e., heart rate, electrocardiogram [ECG], blood pressure, subjective symptoms, pulse oximetry).
- Criteria for test termination.

Subjects will be given time to ask questions prior to initiating the exercise test. Detailed instructions for subject preparation prior to and upon arrival to the exercise testing laboratory will be provided in the Exercise Test Manual.

Supplemental oxygen is not allowed during the 3 phases of the exercise test (i.e., pre-exercise, exercise and recovery phases; see below). Subjects using supplemental oxygen should stop oxygen flow while seated and SpO_2 should be monitored.

All subjects should wait for at least 15 minutes and until a stable oxygen saturation of >85% for 5 minutes has been achieved, whichever is longest, before the pre-exercise phase is initiated. Oxygen saturation stability is defined as a change of ≤2% points over 5 minutes. If the stability criterion is not met after 15 minutes the resting period should be prolonged with 5 minutes at a time, until stability is confirmed.

The test should not be initiated if the subject has an SpO_2 ≤85% at rest, or if desaturation to ≤85% occurs after supplemental oxygen is discontinued.

The exercise test consists of 3 phases:

- Pre-exercise phase monitoring (i.e., heart rate, ECG, blood pressure, pulse oximetry, and symptoms) with collection of data at rest. Duration 5 minutes.
- Exercise phase with controlled ramp-up exercise, increasing speed and gradient on the treadmill every 30 seconds. The initial stage is at 1 mph with no incline. For each stage, the speed is increased by 0.1 mph and the gradient by 0.5%. The full protocol comprises 31 stages (total duration of exercise phase is 15 minutes and 30 seconds) (Section 10.2.2). Subjects will be encouraged to exercise until they achieve maximal effort. The subject may request to stop the test at any time. The exercise test will be terminated prior to maximal effort if absolute termination criteria (e.g., drop in systolic blood pressure, ventricular arrythmia, and ST segment depression) develop.
- Recovery phase: If the test is not terminated prematurely, the first two minutes of recovery will consist of walking at 1 mph and 0% gradient followed by passive recovery for 4 minutes. If no abnormal signs/symptoms develop, total duration of the monitored (i.e., heart rate, ECG, blood pressure, pulse oximetry and symptoms) recovery phase is 6 minutes. Monitoring may continue past 6 minutes if abnormal signs/symptoms persist.

Safety criteria for exercise test termination according to the American Heart Association guidelines (e.g. drop in systolic blood pressure, ventricular arrythmia, and ST segment depression) (Fletcher et al. 2013) will be described in the Exercise Test Manual. The test will be terminated on subject's request in case of intolerable symptoms, e.g., dyspnea, leg fatigue, or angina. An additional criterion of desaturation to SpO_2 ≤80% will be applied (Ross 2003). A termination criterion for heart rate will not be applied given that the standard equations to calculate maximal heart rate according to age are inaccurate on the individual level (Arena, Myers, and Kaminsky 2016).

The following data will be collected during the test at the timepoints specified in Section 10.2.2:

- Current use of betablocker (name / dose)
- Heart rate
- Blood pressure (systolic / diastolic)
- Rating of Perceived Exertion (RPE) (Borg RPE Scale®, scale from 6-20; Section 10.2.3)
- Dyspnea (Borg CR Scale® [CR10], scale from 0-absolute maximum; Section 10.2.4)
- Angina (Angina scale from +1 to +4, or no angina; Section 10.2.5)
- Oxygen saturation (%)
- Time of stopping the test (last stage, seconds completed at last stage) and reason for stopping
- Any symptoms or abnormalities observed during or after the test

ECG should be monitored in all phases of the test and an ECG summary sheet should be uploaded to the eCRF. Printed 12-lead ECGs at rest and every minute of exercise and monitored recovery should be stored at the exercise testing laboratory. ECG abnormalities present at rest or

developed during the exercise test or recovery should be documented on the ECG summary sheet. If the exercise test was terminated due to ECG abnormalities, this should be documented on the ECG summary sheet.

Heart rate, blood pressure, SpO_2 and subjective symptom data as well as the ECG summary sheet will be reviewed by an expert central overreader to ensure that all data points are within expected physiological range. Values falling outside the expected physiologic range will be discussed with the exercise testing laboratory and considered invalid upon agreement with the facility.

Based on the collected data, the following parameters will be calculated:

- Whether sufficient effort during exercise testing was achieved or not (according to criteria below) – to be confirmed by the central overreader.
- Peak MET (using an established equation based on the speed and grade of the last stage the subject was able to complete for at least 15 seconds). The following validated equation to calculate peak METs will be used:

  Peak METs = (speed X (0.17 + fractional grade X 0.79) +3.5)/3.5. Note: Speed in meters/minute (Kokkinos et al. 2017).
- Distance walked.
- Duration of exercise.

The scores from the Borg CR Scale® will be used to investigate changes in dyspnea during the trial.

The criterion for achieving maximal EC is one or more of the following:

- Termination of the exercise test due to desaturation to SpO_2 ≤80%
- For subjects not prescribed a betablocker, termination due to any criteria other than desaturation together with attainment of a maximal exercise heart rate ≥80% of the age-adjusted predicted maximum (220 – Age) (Fletcher et al. 2013).
- For subjects prescribed a betablocker, termination due to any criteria other than desaturation together with attainment of a maximal exercise heart rate ≥65% of the age-adjusted predicted maximum (220 – Age) (Hung et al. 2016).

After completion of the exercise test, the PGIS and PGIC (at post-baseline visits) will be completed (see Section 8.2.12).

Any abnormalities observed during the exercise test will be reported to the Investigator who will assess the abnormality as ‘clinically significant’ or ‘not clinically significant’. All clinically significant abnormalities must be recorded as AEs.

8.2.4. Whole Lung Lavage (WLL)

The need for rescue therapy will be assessed by the frequency of WLL. At each visit, information on whether WLL is required will be evaluated by the Investigator and will be recorded in the eCRF.

The reason(s) for WLL performed will be documented in the eCRF. In addition, the following information will be entered: date and type of WLL (right and/or left lung), amount of saline used,

and time used for performing the WLL. Segmental or lobar lavages will also be recorded on the WLL eCRF page, if used as therapy of aPAP according to local practice.

8.2.5. High Resolution Computed Tomography (HRCT)

As a measure of surfactant accumulation, ground glass opacity (GGO) will be assessed. For this purpose, an HRCT scan will be collected at the timepoints shown in the SoA (Section 1.3) and uploaded into a central database for evaluation of GGO. In order not to unnecessarily increase radiation exposure, chest X-rays are not mandated during the trial.

The fundamental pathological defect in aPAP is surfactant accumulation over time, which can be indirectly assessed by HRCT scan of the chest. Chest CT scans in aPAP shows characteristic findings of GGO with intralobular lines and interlobular septal thickening, often in polygonal shapes (Trapnell and McCarthy 2019; Lee et al. 1997). A semi-quantitative assessment of GGO was introduced by Akira et al (Akira et al. 2000) and subsequently adapted for use in PAP by Tazawa et al (Tazawa et al. 2010).

The extent of GGO will be scored in 3 zones (upper, middle and lower parts) on a scale from 0-5:

0 – No GGO

1 - <5% GGO

2 – 5-24% GGO

3 – 25-49% GGO

4 – 50- 74% GGO

5 - ≥75% GGO

The GGO scores will be assessed by two independent readers with expertise in radiological diagnosis of PAP. The readers will be blinded to subjects' treatment assignment and sequence of the assessed scans (not applicable for the Week 144 HRCT). The total GGO score is calculated by summing up zonal GGO scores (i.e., total GGO score ranges from 0-15). The average total GGO score of the two readers will be used in the statistical analysis.

Furthermore, based on the local radiologic assessment, the HRCT scans will be classified by the Investigator as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. All clinically significant abnormalities will be recorded as AEs except conditions known or diagnosed prior to the trial and observed at Screening Visit 2, which will be recorded as medical history.

The scans may further be evaluated using the automated parenchymal Pattern Analysis using the Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) software (McCarthy et al. 2019). Densitometry assessments of the scans may also be performed. These assessments may be reported separately from the clinical trial report.

8.2.6. Supplemental Oxygen Use

As a clinically meaningful variable, the use of supplemental oxygen during the trial will be assessed at the timepoints shown in the SoA (Section 1.3).

Subjects on supplemental oxygen will be asked to complete a daily oxygen diary in the eDiary. Subjects start completing the eDiary 14 days prior to a visit (Section 10.2.6). If a visit date is rescheduled, the actual number of days of data collection may be less or more than 14 days. The eDiary will capture information on oxygen flow at rest, during sleep, and during exertion, and hours of oxygen use during exertion.

The data from the eDiary will be combined into an oxygen index approximating the average use in liters per minute, assuming that oxygen use during rest equates to 24 hours per day, oxygen use during sleep to 8 hours per day, and oxygen use during exertion to the reported number of hours.

At each visit, the Investigator will further evaluate the current need for supplemental oxygen and enter the following information in the eCRF:

- Oxygen use during exertion, sleep and rest
- Flow rates

The need for supplemental oxygen will be evaluated by the Investigator and the criteria for using oxygen should be entered in the eCRF:

- Resting partial pressure of oxygen (PaO_2) ≤55 mmHg (7.3 kPa)
- Resting PaO_2 ≤60 mmHg (8 kPa) and hematocrit (Hct) ≥55%
- Other

8.2.7. Biomarkers

Blood samples for assessment of the following aPAP-related biomarkers will be taken at the timepoints shown in the SoA (Section 1.3):

- Krebs von den Lungen-6 (KL-6)
- Cytokeratin 19 fragments (CYFRA 21-1)
- Carcinoembryonic antigen (CEA)
- Lactate dehydrogenase (LDH)
- Hb and Hct

Analysis of these biomarkers will be performed by a central laboratory using validated methods. LDH will be analyzed from the standard biochemistry safety laboratory sample, and Hb and Hct from the standard hematology safety laboratory sample.

8.2.8. Biobank

Blood samples for storage in a biobank will be taken at the timepoints shown in the SoA (Section 1.3). Samples will only be taken from subjects who have signed a separate biobank consent. The biobank sample may be used for further exploratory analyses on biomarker variants or other variables thought to play a role in aPAP, or for further analyses of variables that may impact safety or efficacy of the IMP.

8.2.9. Arterial Blood Gas Assessments

The following variables will be assessed from an arterial blood gas sample collected on room air at the timepoints shown in the SoA (Section 1.3):

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

In addition, the resting respiration rate (breaths per minute) will also be assessed in connection with the arterial blood gas sampling.

All subjects should rest in a supine position for at least 15 minutes prior to the arterial blood gas sampling. Subjects on supplemental oxygen should discontinue their oxygen supply at the start of this 15-minute resting period. During this period, oxygen saturation is monitored and recorded every 5 minutes and must be stable prior to initiating the arterial blood gas sampling. Oxygen saturation stability is defined as a change of ≤2 % points over 5 minutes. If the stability criterion is not met after 15 minutes, the resting period should be prolonged with 5 minutes at a time, until stability is confirmed. If a subject does not tolerate discontinuation of oxygen until stabilization, the arterial blood gas sampling will not be conducted. The reason for missing data must be recorded.

Syringes with vented tip caps should be used. The sample must be visually inspected immediately after sampling and bubbles should be expelled immediately after sampling and before mixing by gently tapping the syringe while holding the syringe with the tip pointed upwards and pressing the piston until all visible air has been expelled from the syringe. After that, the cap must be placed on the tip immediately. The blood should be analyzed immediately; no later than 15 minutes after sampling.

PaO_2 will be used for allocating subjects into Disease Severity Score (DSS) categories (Section 8.2.10).

The Investigator must evaluate the PaO_2 result before the subject leaves the clinic and compare this to the oxygen saturation value obtained during the procedure. At the Baseline visit and Visit 9 (Week 24), the test must be repeated if a suspected preanalytical error has occurred. Pre-analytical errors may include:

- Sample contamination with venous blood
- Air-bubble in the syringe
- Clotted sample

As a measure of gas exchange, the A-a gradient (i.e., the A-aDO_2) will be calculated. The A-aDO_2 will be valuable for comparability due to its use as the primary efficacy variable in MOL-PAP-002. The A-a gradient will be calculated centrally using the following formula:

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

Note. P_{atm} (ambient atmospheric pressure) will be recorded. The PH_2O (saturated vapor pressure of water at body temperature) will be set to 47 mmHg/6.266 kPa. The F_iO_2 (fraction of inspired oxygen) will be set to 0.21.

8.2.10. Disease Severity Score (DSS)

As a measure of disease severity, DSS will be assessed at the timepoints shown in the SoA (Section 1.3).

As defined by Inoue et al (Inoue et al. 2008), and elsewhere, the DSS score ranges from 1 (least severe) to 5 (most severe) and is based on patient symptoms and PaO_2 (assessed at rest on room air) as follows:

- DSS 1 PaO_2 ≥70 mmHg and without symptoms
- DSS 2 PaO_2 ≥70 mmHg and with symptoms
- DSS 3 70 mmHg >PaO_2 ≥60 mmHg
- DSS 4 60 mmHg >PaO_2 ≥50 mmHg
- DSS 5 50 mmHg >PaO_2

8.2.11. Clinician's Global Impression of Severity (CGIS) and Change (CGIC)

As measures of overall clinician rated disease severity and treatment response, the Investigator will assess CGIS and CGIC at the timepoints shown in the SoA (Section 1.3, Section 10.2.11).

The current severity of aPAP (CGIS) will be assessed on five-point scale ranging from none, mild, moderate, severe, to very severe.

The change from baseline in aPAP severity (CGIC) will be assessed on a five-point scale ranging from much improved, somewhat improved, no change, somewhat worse, to much worse.

8.2.12. Patient's Global Impression of Severity (PGIS) and Change (PGIC)

PGIS and PGIC will be assessed in the eDiary in relation to and immediately after the SGRQ and treadmill test, respectively, at the timepoints shown in the SoA (Section 1.3).

PGIS will assess the current breathing problems and the impact of these on daily physical activity (after the SGRQ; Section 10.2.7) and current exercise ability (after the exercise test; Section 10.2.8). PGIC will assess the change from baseline in breathing problems and impact of these on daily physical activity (after the SGRQ) and change from baseline in exercise ability (after the exercise test).

In addition, at Week 12, Week 24 and Week 48 subjects reporting worsening or improvement in PGIC will be asked if the change was important to them or not.

8.2.13. Exit Interviews

An exit interview will be performed at Week 24 to qualify the subjects' perception of the meaningfulness of observed changes from baseline and to understand the burden of treatment. An exit interview protocol and guide will be developed. The interview will be performed as a phone interview by a trained interviewer with subjects at prospectively selected sites in North America and/or Europe. The exit interviews will be recorded and transcribed. The results from the exit interviews will be reported separately.

Interviewers will be trained on AE handling. Potential AEs identified during the exit interviews will be forwarded to the site and the investigator should evaluate if an AE form should be completed in the eCRF.

8.3. Safety Assessments

The safety objectives of the trial will be assessed by using the following variables:

- Frequencies of (S)AEs, (S)ADRs, adverse events of special interest (AESIs), deaths and AEs leading to withdrawal from trial and/or permanent discontinuation from treatment. These variables are dealt with in Section 8.4 and Section 8.11.3.
- Development of treatment-boosted anti-GM-CSF antibody titers
- Spirometry (Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1) and FEV_1/FVC)
- Change in QT interval corrected by Fridericia (QTcF)

Although not included as formal safety endpoints of the trial, subject safety will also be assessed by physical examinations, ECG, vital signs, body weight and clinical safety laboratory assessments. In addition, pregnancy screen and check of contraceptive use will be performed.

In the event of a COVID-19 outbreak impacting patients participating in the trial, the Sponsor will work with any impacted sites on appropriate mitigation procedures.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Electrocardiograms

Three (3) unique, resting, 12-lead ECG assessments will be obtained using centrally provided ECG equipment at the time points shown in the SoA (Section 1.3.1). After Week 48 (and upon implementation of protocol version 10.0), a single resting, 12-lead ECG assessment will be obtained at the time points shown in the SoA (Section 1.3.2).

ECGs collected at baseline, Week 4 and Week 24 will be overread by a central ECG laboratory using a limited number of readers overseen by a cardiologist. R-R, PR, QRS, and QT intervals will be determined on 3 consecutive beats in Lead II, or an alternative lead if Lead II is not acceptable for measurement. Mean RR, PR, QRS, QT, QTcB, QTcF and heart rate will be calculated. The cardiologist will conduct standard interpretation of the ECGs as normal/abnormal

and type of abnormality. The ECG procedures will be described in an ECG manual. Cardiologist reports will be reviewed, signed and dated by the Investigator or his/her designee.

All ECGs collected will be interpreted and signed and dated by the Investigator or his/her designee. Any abnormalities will be recorded in the eCRF and assessed as 'clinically significant' or 'not clinically significant'. In case of discrepancy between the cardiologist and the Investigator assessment, the Sponsor should be contacted to facilitate resolution. Abnormalities classified as 'clinically significant' will be recorded as AEs except those observed at Screening Visit 1 which will be recorded as medical history.

8.3.2. Physical Examinations

All subjects will undergo physical examinations at the timepoints shown in the SoA (Section 1.3).

Full physical examinations will include at a minimum:

- A review of the subject's general appearance
- Head, eyes, ears, nose, and throat
- Neck
- Heart and lungs
- Abdomen
- Extremities
- Skin
- General neurological system.

Any abnormalities will be recorded in the eCRF and assessed as 'clinically significant' or 'not clinically significant'. Abnormalities classified as 'clinically significant' will be recorded as AEs except those observed at Screening Visit 1 which will be recorded as medical history.

Symptom-oriented or brief physical examinations, as clinically indicated, will be performed at the timepoints shown in the SoA (Section 1.3). New abnormal clinically significant physical examination findings which were not present during the Screening Visit 1 should be recorded as AEs and followed during subsequent visits.

8.3.3. Vital Signs and Body Weight

The following parameters will be assessed at the timepoints shown in the SoA (Section 1.3).

- Resting systolic and diastolic blood pressure (mmHg), after 5 minutes sitting
- Resting heart rate (beats per minute), after 5 minutes sitting
- Body temperature (°C)
- Body weight (kg) in indoor clothes without shoes

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

abnormalities will be recorded as AEs except those observed at Screening Visit 1 which will be recorded as medical history.

8.3.4. Clinical Safety Laboratory Assessments

See Section 10.3 for a list of clinical laboratory tests (hematology, biochemistry, and urinalysis) to be performed and to the SoA (Section 1.3) for the timing and frequency of the assessments.

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

The reported results will be recorded and assessed as 'normal' or 'abnormal'. Abnormal results will be assessed by the Investigator as 'clinically significant' or 'not clinically significant'. All clinically significant abnormalities will be recorded as AEs except those observed at Screening Visit 1 which will be recorded as medical history.

8.3.5. Pregnancy Test

Serum pregnancy tests will be performed for women of childbearing potential at all visits during the double-blind and open-label treatment periods except for the Week 52 telephone visit. In addition, a urine pregnancy test will be performed before dosing at the Baseline visit (Visit 3) to immediately confirm that the subject is not pregnant. A contraceptive check of both male and female subjects will also be performed at all visits.

For visits with 12-week intervals (i.e., visits after Week 24), women of childbearing potential should also check pregnancy at home with monthly urine dipstick pregnancy tests. Date of the dipstick test should be recorded in the Subject instructions and diary (Section 8.12). Results of the pregnancy tests (on-site and at home tests) will be entered in the eCRF.

8.3.6. Anti-GM-CSF Antibodies

Blood sampling for assessment of diagnostic anti-GM-CSF autoantibodies will be performed at Screening Visit 1. In addition, blood sampling for assessment of treatment-boosted anti-GM-CSF antibodies will be performed at time points shown in the SoA (Section 1.3).

Analyses for diagnostic anti-GM-CSF antibodies will be performed at three regional central laboratories (in the US, Europe, and Japan). The cut-off values for diagnostic levels of anti-GM-CSF autoantibodies will be according to clinical standards at the regional central laboratories.

The titer of anti-GM-CSF antibodies over the course of treatment until 4 weeks after end of treatment will be analyzed at a central specialized laboratory.

Anti-excipients antibodies (including immunoglobulin types) and the neutralizing capacity of anti-GM-CSF antibodies measured by cell-based methods may also be analyzed according to a separate bioanalysis plan.

8.3.7. Spirometry (FVC, FEV_1 and FEV_1/FVC)

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) will be assessed at the time points shown in the SoA (Section 1.3). Spirometry will be conducted prior to the DLCO, using the same equipment.

FEV_1 and FVC will be performed in accordance with ATS/ERS guidelines for spirometry testing (Miller et al. 2005). At least three acceptable and repeatable maneuvers according to ATS/ERS criteria are required. Up to eight maneuvers may be conducted, if needed, during a session. The largest FEV_1 and FVC will be used in the analyses. Standardization across sites will be obtained by using the same equipment and implementing central overread by a team of external, independent respiratory experts. Predicted values will be calculated by the centrally provided equipment according to the Global Lung Function Initiative prediction equations (Quanjer et al. 2012). A manual will be provided to all trial sites that will describe the spirometry test in more detail.

A drop of ≥10% predicted in either FEV_1 or FVC between two visits should be evaluated for clinical significance by the Investigator. All clinically significant changes should be recorded as AEs.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE.

AEs and SAEs will be collected from the signing of the ICF until the Week 148 visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before signing the ICF will be recorded as medical history.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4.4. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively report new AEs or SAEs for subjects who have completed or are withdrawn from the trial. However, if the Investigator learns of any SAE, including a death, at any time after a subject has completed or been withdrawn from the trial, and he/she considers the event to be reasonably related to the IMP or trial participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Recording and Assessing AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up at subsequent visits/contacts on all AEs until either resolution or until judged by the Investigator to be stable/needing no further follow-up. Further information on follow-up procedures is provided in Section 10.4.3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it in the Investigator trial master file (TMF) and will notify the IRB/IEC, if appropriate according to local requirements.

SAEs qualifying as SUSARs are subject to a 7-day reporting timeframe for life-threatening and fatal SUSARs and a 15-day reporting timeframe for all other SUSARs. Investigator safety reports will be prepared by the Sponsor for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators, as necessary.

In the European Union (EU), SUSARs will be registered in EudraVigilance as applicable. Once a year, a development safety update report (DSUR) will be submitted to competent authorities and IECs via the Clinical Trial Information System (CTIS).

8.4.5. 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 have their IMP discontinued. Male and female 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 10.4.4. The pregnancy report form should be used instead of the SAE form.

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

8.4.6. Adverse Events of Special Interest

The following AEs have been identified as AESIs with need for additional data collection, which may include additional investigations when required, to further characterize and understand them:

- Hypersensitivity reaction

  Subjects will be observed for any hypersensitivity reactions for 1 hour after the first dose. If a subject develops a type I hypersensitivity reaction further dosing should be suspended, permanently or temporarily, according to Investigator's judgment. The subject should be contacted by phone 8-12 hours after the event to check for any delayed reaction. Subjects experiencing serious hypersensitivity reactions will be discontinued from the trial.

- Chest pain

  All subjects should be instructed to call the site if chest pain develops, and based on the information provided over the phone, additional investigations, e.g., ECG and chest X-ray, may be conducted according to Investigator's judgment.

The events may be serious or non-serious and must follow the standards for AE/SAE reporting as described above. In addition, a specific form for each type of event must be filled out within the time frame as for other AE/SAEs as specified in Section 8.4.1.

In case the Sponsor identifies potentially missed AESIs through predefined review of available data, the Investigator will be asked to reconsider if this is an AESI.

8.5. Treatment of Overdose

Molgramostim nebulizer solution in doses of 600 µg once daily for 6 days have been administered via inhalation to healthy volunteers without any safety concerns. In the present trial, in the event of an overdose, as judged by the Investigator, the event should be reported as an AE and supportive treatment or discontinuation of the IMP may be applied as judged by the Investigator.

8.6. Pharmacokinetics

Pharmacokinetic samples will be collected at the timepoints shown in the SoA and the time of sampling will be recorded.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this trial.

8.8. Genetics

Genetics are not evaluated in this trial.

8.9. Biomarkers

See Section 8.2.7.

8.10. Immunogenicity Assessments

See Section 8.3.6.

8.11. Health Economics and Quality of Life

8.11.1. EuroQoL 5 Dimensions, 5 Levels (EQ-5D-5L)

Subjects will complete the EQ-5D-5L questionnaire in the eDiary, after the SGRQ, before other trial assessments, at the time points shown in the SoA (Section 1.3).

The EQ-5D-5L is a generic, multidimensional, health-related, quality-of-life instrument and comprises a Visual Analogue Scale (VAS) and a short descriptive system questionnaire. The VAS provides an alternative way to elicit a subject's rating of his/her own overall current health. The questionnaire provides a simple descriptive profile of a respondent's health state.

The VAS records the subject's overall current health on a vertical VAS where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS provides a quantitative measure of the subject's perception of his/her overall health.

The descriptive system allows subjects to rate their health in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a 5-level scale indicating: 1. No problem, 2. Slight problem, 3. Moderate problem, 4. Severe problem or 5. Unable to/extreme problems (Section 10.2.9). The perceived problem levels for each domain are combined into a 5-digit health state that is converted to an index value which reflects how good or bad a health state is according to the preferences of the general population, with higher scores indicating better quality of life.

8.11.2. Patient Journey

As a description of burden of disease in terms of relevant patient experiences from first symptoms and diagnosis up to the time of the trial, a sheet to capture such information (Section 10.2.10) will be handed out to the subject at Screening Visit 2 and returned completed at the Baseline visit. The site will upload a pdf copy of the completed sheet to the eCRF. The results from the Patient Journey assessments are intended for use in e.g., health economic evaluations and will not be included in the clinical database.

8.11.3. Hospitalizations

If a subject is hospitalized during the trial, the following information will be collected in the eCRF:

- Admission diagnosis

- Admission date
- Admission facility/ward (e.g., intensive care unit, emergency room, pulmonary department, other specified)
- Any invasive aPAP-related treatment during admission (e.g., WLL, ventilator, other specified)
- Discharge status (e.g., recovered, in recovery, unchanged, deteriorating)
- Discharged to e.g., nursing home, home, other hospitalizations
- Discharge date

Ambulatory hospitalizations will not be collected in the eCRF.

8.12. Subject Instruction and Diary

At the time points shown in the SoA (Section 1.3), subjects will receive a Subject Instruction and Diary. The subject should hand-back the Subject Instruction and Diary at the following visit. The Subject Instruction and Diary will include information about assessments at the next visit and details about the handling of the IMP. The subject will be asked to complete information about dates for starting on new IMP kits, cleaning of the nebulizer, change of nebulizer handsets, dates for taking pregnancy test (if applicable) and any potential AEs experienced by the subject between the visits.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock and subsequent unblinding of trial treatment codes and it will include a more technical and detailed description of the statistical analyses described in this section. The following sections are a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1. Statistical Hypotheses

The primary null hypothesis is that there is no difference between MOL and PBO in the mean change from baseline to 24 weeks in % predicted DLCO.

The alternative hypothesis is that there is a difference between MOL and PBO in the mean change from baseline to 24 weeks in % predicted DLCO.

9.2. Sample Size Determination

Based on data from MOL-PAP-002, the sample size was estimated for the primary endpoint assuming a treatment effect for change from baseline to Week 24 in DLCO of 5.7 percentage points, a standard deviation (SD) of 11 percentage points and a significance level of 5%. With a total of 160 randomized subjects, assigned at a 1:1 ratio to double-blind treatment per treatment group, the power for showing an effect on DLCO is 90%.

In addition, a blinded sample size re-assessment will be conducted by the Sponsor (or delegate) after 80 subjects have completed the Week 24 visit. Using the estimate of variance and an assumed effect size of 5.7 percentage points, a sample size calculation will be performed to determine if the sample size should be increased. The calculations will be based on having 90% power for the primary endpoint.

A short report will be prepared to document the sample size re-assessment process and results. The sample size re-assessment report will be included in the trial documentation.

The Sponsor will remain blinded to the treatment allocations throughout the process of sample size re-estimation.

9.3. Trial Estimands

The following sections describe the attributes of the estimands that will be used for evaluation of the primary endpoint and similar principles that will be applied for the secondary efficacy endpoints.

9.3.1. Estimand for the Primary Endpoint

9.3.1.1. Treatment

The treatment is molgramostim nebulizer solution administered by inhalation once daily over a period of 24 weeks, which will be compared to placebo inhalation. Both interventions will be applied on top of standard of care that includes supplemental oxygen when required and rescue treatment with WLL in case of worsening, but not off-label treatments like GM-CSF or rituximab.

9.3.1.2. Population

The primary analysis will be performed in all randomized subjects, who represent a population of adult patients with a confirmed diagnosis of aPAP as defined by the trial population inclusion/exclusion criteria.

9.3.1.3. Patient-level Endpoint

For each patient, efficacy will be measured using the primary endpoint of absolute change in % predicted DLCO from baseline to Week 24. The calculation requires an acceptable and repeatable maneuver at baseline and Week 24, including the required discontinuation of supplemental oxygen for 15 minutes prior to the assessments.

9.3.1.4. Intercurrent Events

Anticipated intercurrent events include rescue therapy (i.e., WLL), supplemental oxygen, off-label treatments, treatment discontinuation, treatment non-compliance, and trial withdrawal:

- For subjects who require supplemental oxygen or a WLL for worsening of aPAP as specified in the clinical trial protocol, outcomes observed during and after the period of this additional treatment are included as they are consistent with the treatment condition under evaluation. Therefore, the treatment policy strategy is planned with respect to these types of events.

  Similarly, if any subjects use prohibited off-label treatments (such as other GM-CSF products or rituximab), outcomes observed during and after the period of this additional treatment are included as such off-label use in clinical practice can be a consequence of the treatment policy.

- For subjects who are non-compliant with the trial intervention, all data will be used, irrespective of compliance. Therefore, the treatment policy strategy is used with respected to this type of event.

- Subjects who discontinue trial therapy for any reason prior to Week 24 will be encouraged to remain in the trial and complete all scheduled assessments and, as a minimum, the Week 24 visit. Data collected before and after treatment discontinuation will be used for the primary analysis. Therefore, the treatment policy strategy is used with respect to this type of event.

- Whilst withdrawal from the trial is not, in itself, an intercurrent event, for subjects who withdraw from the trial or are lost to follow-up prior to Week 24, their Week 24 data will be imputed using control-based multiple imputation. (Note that this could include, for example, patients who have a WLL and who may subsequently withdraw from the trial prior to Week 24, or those who discontinue therapy and who may subsequently withdraw from the trial prior to Week 24). The rationale for this imputation is based on the assumption that trial withdrawal may be related to lack of efficacy, desire to initiate off-label treatment, or adverse events, and therefore it is assumed that patients who drop out of the trial will not show a Week 24 benefit.

- For subjects who worsen to the extent that DLCO cannot be adequately conducted according to ATS/ERS guidelines at Week 24, although expected to be a very rare event,

their Week 24 data will be imputed using control-based multiple imputation. This is based on the assumption that this degree of worsening indicates that the subject did not have treatment benefit at Week 24.

9.3.1.5. Population-level Summary

On the population level, the difference in Lsmean change in DLCO % predicted from baseline to Week 24 will be used to compare the treatment groups.

9.3.2. Estimands for the Secondary Efficacy Endpoints

For secondary efficacy endpoints, similar principles will be applied as for the primary efficacy endpoints with further details included in the SAP, which will be finalized before unblinding. For example, replacing Week 24 by Week 48 (where applicable).

As for DLCO, for subjects who worsen to the extent that the exercise test cannot be initiated with the subject breathing room air due to worsening of aPAP, their Week 24 data will be imputed using control-based multiple imputation. This is based on the assumption that this degree of worsening indicates that the subject did not have treatment benefit at Week 24. Corresponding imputation will be done for DLCO and for the exercise test at Week 48 (further details in the SAP).

Only applicable for Japan and South Korea:

- *Intercurrent Events: For subjects who worsen to the extent that blood gas sampling cannot be conducted with the subject breathing room air, although expected to be a very rare event, their Week 24 data will be imputed using control-based multiple imputation. This is based on the assumption that this degree of worsening indicates that the subject did not have treatment benefit at Week 24.*

9.4. Populations for Analyses

The analysis populations are defined in Table 5. Although efficacy summaries will be performed on both the Full Analysis Set (FAS) and the Per-protocol Set (PPS), the FAS will be considered the primary analysis population. Safety summaries will be performed on the safety analysis set (SAS).

Table 5: Analysis Populations

Population	Description
Screened	All subjects who sign the informed consent form.
Full analysis set (FAS)	All subjects randomized. Subjects will be analyzed according to the randomized treatment.
Per-protocol set (PPS)	All randomized subjects who have completed 24 weeks' double-blind treatment (Visit 9) and are deemed to have no important protocol deviations that could interfere with the objectives of this trial. Important deviations of eligibility criteria and other deviations from the protocol will be assessed. Important deviations from the protocol may

Population	Description
	lead to exclusion of a subject or data points from the PPS. All such decisions will be made and documented before the final trial database is unblinded.
Safety analysis set (SAS)	All subjects randomized and who take at least 1 dose of IMP. Subjects will be analyzed according to the IMP they actually received.

9.5. Statistical Analyses

9.5.1. General Considerations

The trial will be unblinded and the primary analysis will be conducted after all subjects have completed the 48-week double-blind period. In addition, a blinded sample size re-assessment will be conducted after 80 subjects have completed the Week 24 visit to evaluate whether the sample size needs to be increased (see Section 9.2).

Before the trial is unblinded for primary analysis, a blind review of the data will be completed. At that time, adjustments to the planned analyses may be identified based on, for example, the extent and timing of missing data. Confirmation of eligibility for analysis populations (see Section 9.4) will be confirmed at this time.

Analyses of data from the first 48 weeks of treatment will be described in the SAP. The data from the open-label period will be presented descriptively.

Baseline measurements are defined as the last measurement taken before randomization, taken either at the screening visits or the Baseline visit.

9.5.2. Type I Error Control

For regulatory authorities outside of Japan or South Korea:
There is one primary efficacy parameter and seven secondary efficacy endpoints which are intended to support conclusions based on the primary parameter. A type I error control procedure that uses a combination of sequential testing and alpha-splitting will be used for analysis of these endpoints to maintain the overall type I error rate at 5%. The procedure is shown schematically in Figure 2 and described beneath the schematic.

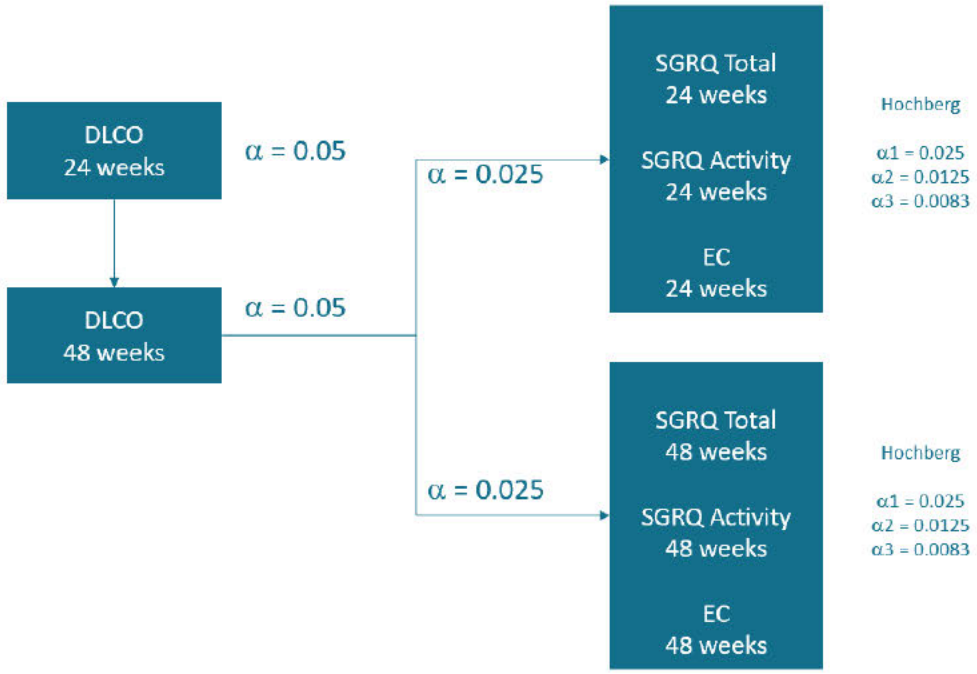


Figure 2: Type I Error Control for Efficacy Endpoints

1. DLCO at Week 24 is tested at two-sided alpha = 0.05 ("Family 1"). If DLCO at Week 24 is not statistically significant then the procedure stops
2. If DLCO at Week 24 is statistically significant then DLCO at Week 48 ("Family 2") is tested at two-sided alpha = 0.05.
3. If DLCO at Week 48 is statistically significant then the 5% alpha is split equally and passed to "Family 3" and "Family 4" which consist of the SGRQ Total, SGRQ Activity and EC endpoints for Week 24 and 48, respectively.
4. The Hochberg procedure (Hochberg 1988) is applied to each of Family 3 and Family 4. Further details will be provided in the SAP.

In addition, several other explorative endpoints will be considered as descriptive and supportive, but no adjustments for multiplicity will be made for these analyses.

Specific for Japan and South Korea:
There is one primary efficacy parameter although there are four secondary efficacy endpoints which are intended to support conclusions based on the primary parameter. A type I error control procedure that uses sequential testing will be used for analysis of these four secondary endpoints to maintain the overall type I error rate at 5%. In addition, several other explorative endpoints will be considered as descriptive and supportive, but no adjustments for multiplicity will be made for these analyses. The type I error control procedure is shown schematically in Figure 3 and described beneath the schematic.

Figure 3: Type I Error Control for Efficacy Endpoints (for Japan and South Korea)

1. *DLCO at Week 24 is tested at two-sided alpha = 0.05 ("Family 1"). If DLCO at Week 24 is not statistically significant then the procedure stops*
2. *If DLCO at Week 24 is statistically significant then the 5% alpha is passed to "Family 2" which consists of the SGRQ Total, SGRQ Activity, EC and A-aDO$_2$ endpoints for Week 24.*
3. *The Hochberg procedure (Hochberg 1988) is applied to Family 2. Further details will be provided in the SAP.*

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

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

9.5.3. Demographic and Other Baseline Characteristics

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

9.5.4. Exposure to Treatment

Exposure to treatment will be presented using summary statistics.

9.5.5. Concomitant Treatment

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

9.5.6. Primary Endpoint – Absolute Change in Percent of Predicted DLCO from Baseline to Week 24

A general linear mixed model for repeated measurements will be used to analyze the primary endpoint and will be fitted with treatment, baseline DLCO % predicted, a binary indicator for DLCO stratification and a 3-level factor for region, and visit as categorical fixed effects, along with a treatment-by-visit interaction term. The estimated treatment effect will be the difference in Lsmean change in DLCO % predicted from baseline to Week 24, taken from the treatment-by-visit interaction term at 24 weeks. Although data is also collected after the Week 24 visit, only data up to Week 24 will be used in the statistical model used for the primary endpoint at Week 24 (i.e., up to Visit 9). The estimated treatment effect will be presented with a 95% confidence interval (CI) and a P-value to test the null hypothesis that the effects of molgramostim and placebo at Week 24 are the same.

The analysis model is:

$$Y_{ijk} = \beta_0 \cdot y_{ij0} + T_i + R_l + S_m + V_k + TV_{ik} + s_{ij} + e_{ijk}$$

where

Y_{ijk} is the % predicted DLCO value for the j^{th} subject of treatment group i at visit k *(where $k=4,\ldots,9$)*

y_{ij0} is the baseline % predicted DLCO value for the j^{th} subject of treatment group i

β_0 is the unknown fixed slope for the baseline DLCO % predicted

T_i is the unknown fixed effect of treatment i

R_l is the unknown fixed effect of regional stratification factors l (0 or 1 or 2)

S_m is the unknown fixed effect of DLCO severity stratification factor m (0 or 1)

V_k is the unknown fixed effect of visit k

TV_{ik} is the unknown fixed interaction effect between treatment i and visit k

s_{ij} is the subject effect associated with the j^{th} subject of treatment i

e_{ijk} is the error (residual) associated with the j^{th} subject of treatment i at visit k

s_{ij} and e_{ijk} are assumed to be independent from each other and follow a multivariate normal distribution. The covariance matrix for e will be the unstructured variance-covariance matrix, since it assumes pair-wise correlations are not constrained by the data.

The estimated treatment effect is taken from the TV_{ik} interaction term at Visit 9 (i.e., 24 weeks).

Any subject with missing % predicted DLCO data will have those missing values imputed using a multiple imputation method, using a conservative control-based rule:

- The missing values are filled in *n* times to generate *n* complete data sets (using SAS PROC MI).

This is done by fitting *n* linear regression models using placebo-only subjects with observed values for the endpoint and further covariates (baseline covariates and measurements of % predicted DLCO at earlier visits; full details of the covariates to be used will be included in the SAP).

Based on the fitted regression model, a new regression model is simulated from the Bayesian posterior predictive distribution of the regression parameters and is used to impute the missing values:

- The *n* complete datasets are analyzed by using the model described above.
- The results from the *n* analyses are combined for statistical inference using Rubin's rules (using SAS PROC MIANALYZE).

Multiple imputation aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. The method assumes that missing values are a result of patients stopping taking their medication and so following a trajectory akin to patients randomized to placebo.

Sensitivity analyses, including tipping point analyses and responder analyses (5-, 7-, and 10-point change in DLCO % predicted) will be described in the SAP. In addition, the SAP will describe sensitivity analyses and estimands that address both COVID-19 pandemic-related and unrelated issues.

9.5.7. Secondary Endpoints

Absolute change in % predicted DLCO from baseline to Week 48 will be analyzed using a similar model as for DLCO at Week 24 but with the Week 48 timepoint used for inference (using data from Visits 4 to 11).

Change from baseline to Week 24 and baseline to Week 48 in SGRQ Total and SGRQ Activity will be analyzed using a similar model as for DLCO at Week 24 and Week 48 respectively except using baseline SGRQ Total or SGRQ Activity as the covariate (y_{ij0}) instead of baseline DLCO.

Change from baseline to Week 24 and baseline to Week 48 in EC (expressed as peak METs) will be analyzed using a similar model as for DLCO at Week 24 and Week 48 respectively except using baseline (measured at Screening Visit 2) peak METs as the covariate (y_{ij0}) instead of baseline DLCO.

Only applicable for Japan and South Korea: Change from baseline to Week 24 in A-aDO_2 will be analyzed using a similar model as for DLCO at Week 24 except using baseline A-aDO_2 as the covariate (y_{ij0}) instead of baseline DLCO.

For Week 24 endpoints, imputation for missing values for all secondary endpoints will follow the same procedure as for the primary endpoint. For Week 48 endpoints, imputation will follow the same principles as for the primary endpoint but will use data up to Week 48 (visits 4 to 11).

Sensitivity analyses, including tipping point analyses, methods for establishing responder thresholds (for SGRQ Total, SGRQ Activity and EC) and corresponding responder analyses will be described in the SAP.

9.5.7.1. Frequencies of (S)AEs, (S)ADRs, AESIs, Deaths and AEs Leading to Withdrawal

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

The total number of subjects with at least one AE, the total number of AEs, and AE event rate will be presented. The number of subjects and the number of AEs will be tabulated by SOC and by PT. AEs will also be tabulated by severity and by relationship.

All SAEs and AEs leading to withdrawal from trial and/or permanent discontinuation from treatment will be fully described in individual subject narratives.

9.5.8. Exploratory Endpoints

The statistical analyses of the exploratory endpoints will be described in the SAP.

9.5.9. Other Safety Analyses

The statistical analyses of other safety endpoints will be described in the SAP.

9.5.10. Other Analyses

The statistical analyses of the health economic and quality of life endpoints will be described in the SAP.

Exit interviews will be analyzed according to a separate SAP.

9.6. Interim Analyses

No Interim Analyses are planned and thus no early stopping for efficacy is intended.

9.7. Data Monitoring Committee

A DMC will be established to perform a safety evaluation during the trial. A DMC Charter will define the primary responsibilities of the DMC, its membership, the purpose and timing of its meetings, and its procedures including those for restricted access to unblinded data.

Safety evaluation on blinded data will also be performed by the Sponsor via regular safety surveillance.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
  - The rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning them are safeguarded according to local regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated. In the EU, these documents must be submitted to the competent authorities and ethics committees via CTIS. The approval of the trial in the EU will also be provided via CTIS.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the site and adherence to pertinent requirements of title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Directive 2001/20/EC or European regulation 536/2014 for clinical studies (as applicable), and all other applicable local regulations

10.1.2. Protocol Compliance

- Serious breaches of the Clinical Trial Regulation no. 536/2014 (EU 2014) or this protocol will be reported to the EU CTIS within seven calendar days (7) after the Sponsor has been made aware of the breach. Serious breaches mean breaches likely to

affect to a significant degree the safety and rights of the subject or the reliability or robustness of the data generated in the clinical trial. Suspected serious breaches should be reported in a timely manner. Savara should be notified of suspected serious breaches within 1 business day of discovery.

10.1.3. Financial Disclosure

- Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.4. Informed Consent Process

- The Investigator or his/her delegate will explain the nature of the trial to the subject or his/her legally authorized representative and answer all questions regarding the trial.
- Subjects must be informed that their participation is voluntary. Prior to participation in the trial, subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act and/or the General Data Protection Regulation requirements, where applicable, and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before the subject was screened and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 8 weeks from the previous ICF signature date.
- The ICF will contain a separate section that addresses the collection and use of additional biobank samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow collection and use of biobank samples for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.5. Data Protection

- The Sponsor will ensure confidentiality of the participants by appropriate technical and organizational safety measures.
- Subjects will be assigned a unique identifier by the Sponsor. The Sponsor will only receive pseudonymized trial data; information related to the subject's identity is kept at the trial site and is not accessible to the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- All data will be handled in accordance with the EU's current Data Protection Law Enforcement Directive, The General Data Protection Regulation and the local data protection regulations. For this trial, the Sponsor and Investigational Site are the data controller of all data processed during the trial and CROs and other sub-contractors used are data processors. In the EU, the contracts between the Sponsor, CRO and other sub-contractors used, and trial sites specify responsibilities of the parties related to data protection, including handling of data subjects' rights and data security breaches as well as respective communication and cooperation of the parties.

10.1.6. Committees Structure

- An independent data monitoring committee (DMC) will perform a safety evaluation during the trial. A separate charter for this committee will be prepared.

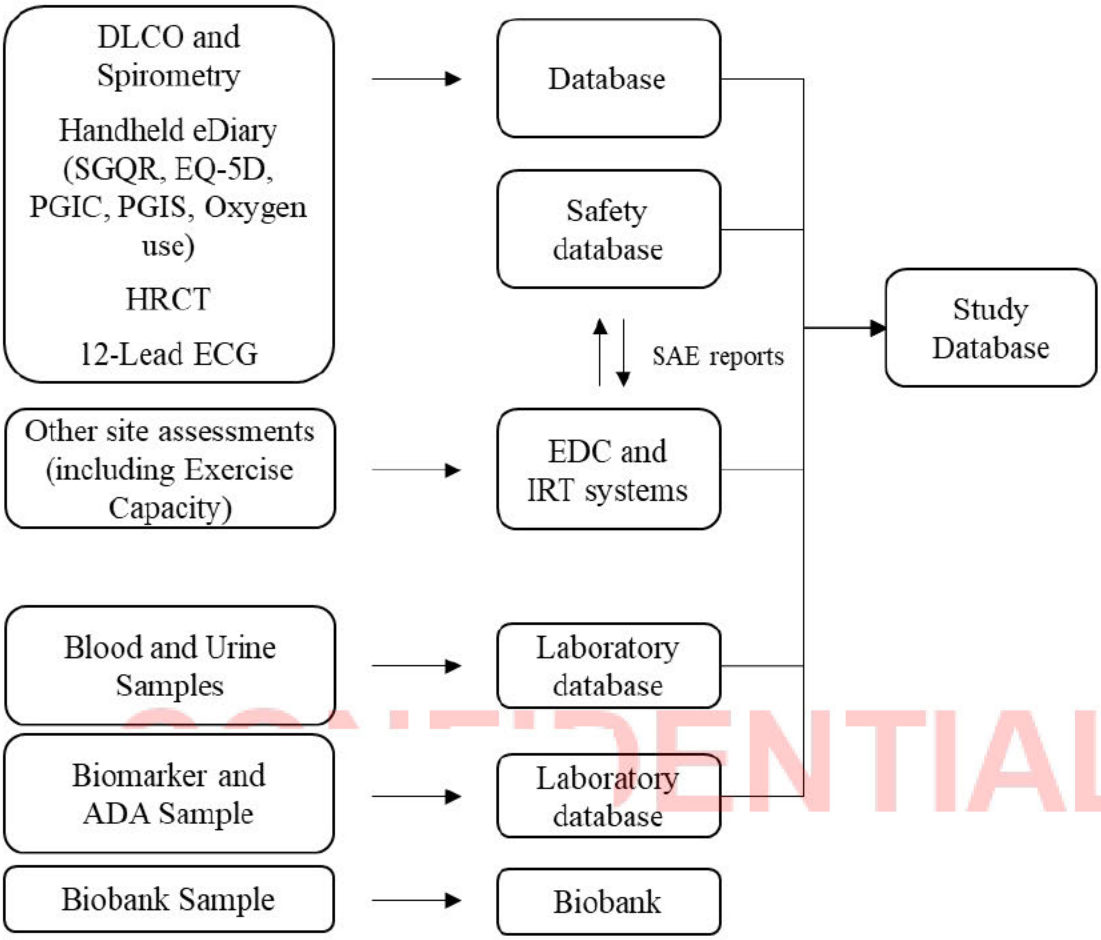
10.1.7. Dissemination of Clinical Trial Data

- The trial results will be posted on www.clinicaltrials.gov and the CTIS Portal in the EUaccording to current regulations.
- Two Clinical Trial Reports (CTRs) will be prepared; both will follow the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3): the first CTR will include the results from the double-blind period and a second CTR will include the results of the open-label period.

10.1.8. Data Quality Assurance

- Subject data will be collected by means of EDC. The overall dataflow is described in Figure 4.

- DLCO, spirometry, imaging, ECG, laboratory data and biomarkers will be collected electronically in separate databases and will be transferred electronically to the Sponsor or designee.
- Data collected in databases other than the eCRF will be reconciled with relevant eCRF data.
- SAE reports will be entered in the eCRF system and/or SAE Report Form and will be transferred to the pharmacovigilance database.
- Pregnancy reports will be handled via paper forms.
- A reconciliation between the eCRF and the pharmacovigilance database will be performed.
- Subject data should be entered into the eCRF as soon as possible after the visit in accordance with the time requirements described in the Clinical Trial Agreement with the site.
- Seemingly non-physiological values will be discussed with the Investigator to evaluate if the values are correct or likely to be erroneous. Data from patient reported outcomes, including eDiary data, will not be queried. Handling of data used for the analyses will be described before unblinding the trial.
- The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.



Abbreviations: ADA= Anti-drug antibody; DLCO=Diffusing capacity of the lungs for carbon monoxide; ECG=Electrocardiogram; EDC=Electronic data capture; EQ-5D=EuroQoL 5 Dimensions; HRCT=High resolution-computed tomography; IRT=Interactive Response Technology; PGIC=Patient's Global Impression of Change; PGIS= Patient's Global Impression of Severity; SAE=Serious adverse event; SGRQ=Saint George's Respiratory Questionnaire.

Figure 4: Overall Data Flow

- Queries for discrepant data may be generated automatically by the system upon entry or generated manually, for example by the CRA, medical monitor or data manager. All queries, whether generated automatically by the system or by a user, will be in an electronic format. This systematic validation will ensure that a clean and consistent database is provided prior to the statistical analysis being performed.
- Patient reported outcome data will be collected at site via an eDiary; a smartphone device provided to the subjects.
- At home, subjects on supplemental oxygen will complete a daily eDiary about their use of supplemental oxygen. The eDiary data collected are not integrated with the

eCRF database but are uploaded to a separate database. Data will be available for the site personnel right after data entry.

- eDiary data will be available immediately after data entry and available for monitors and site personnel, including the Investigator, with read access only. The Investigator (or designee) is expected to review eDiary data and remind and re-train the subject if appropriate to ensure data completeness.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- In exceptional circumstances, such as a local outbreak of COVID-19, the Sponsor will determine the extent and nature of any remote source data verification that is needed for the trial in the specific situation and will carefully weigh it against the extra burden for the site staff and facilities. The Investigator will at all times determine whether the situation at their clinical site allows any of the guideline recommended options for remote source data verification (e.g., sharing of pseudonymized copies, controlled remote access to electronic records, or video review of records with site staff support) without compromising patient care or subject integrity.
- Monitoring details describing strategy (e.g., risk-based initiatives), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, and on-site monitoring) are provided in the Monitoring Plan
- The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organization personnel).
- Trial monitors will perform ongoing source data review/verification in accordance with a monitoring manual to confirm that data entered into the eCRF by authorized site personnel is accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. However, the medical files of trial subjects shall be archived in accordance with national law. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

- The Sponsor is responsible for archiving the content of the clinical TMF for at least 25 years after completion of the trial (i.e., last subject last visit).
- For archiving purposes, each investigator will be supplied with a copy of the data collected for all subjects (including screen failures) at the trial site. This is done after completion of the trial and before site access to the eCRF and eDiary databases are revoked. Audit trail and query information will be included. eCRFs, ePROs, eDiaries must be available for inspection by authorized representatives from Savara, from regulatory authorities and/or IEC/IRBs.
- Exit interviews will be collected over the phone and transcripts will be prepared. The transcripts will be archived together with the trial data.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Source data should as a rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified (Sub)investigators.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents. The Investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There must only be one source defined at any time for any data element.
- Randomization is performed in the IRT system, which is integrated with the eCRF database. No other source data will be entered directly in the eCRF.
- Source data will be captured directly for selected assessments e.g., DLCO, spirometry, eDiary, ECG and laboratory assessments. These assessments are captured electronically and will be stored in databases separately from the eCRF.

10.1.10. Trial and Site Closure

- The Sponsor reserves the right and sole discretion to close the trial site or terminate the trial at any time for any reason. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.
- The Investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

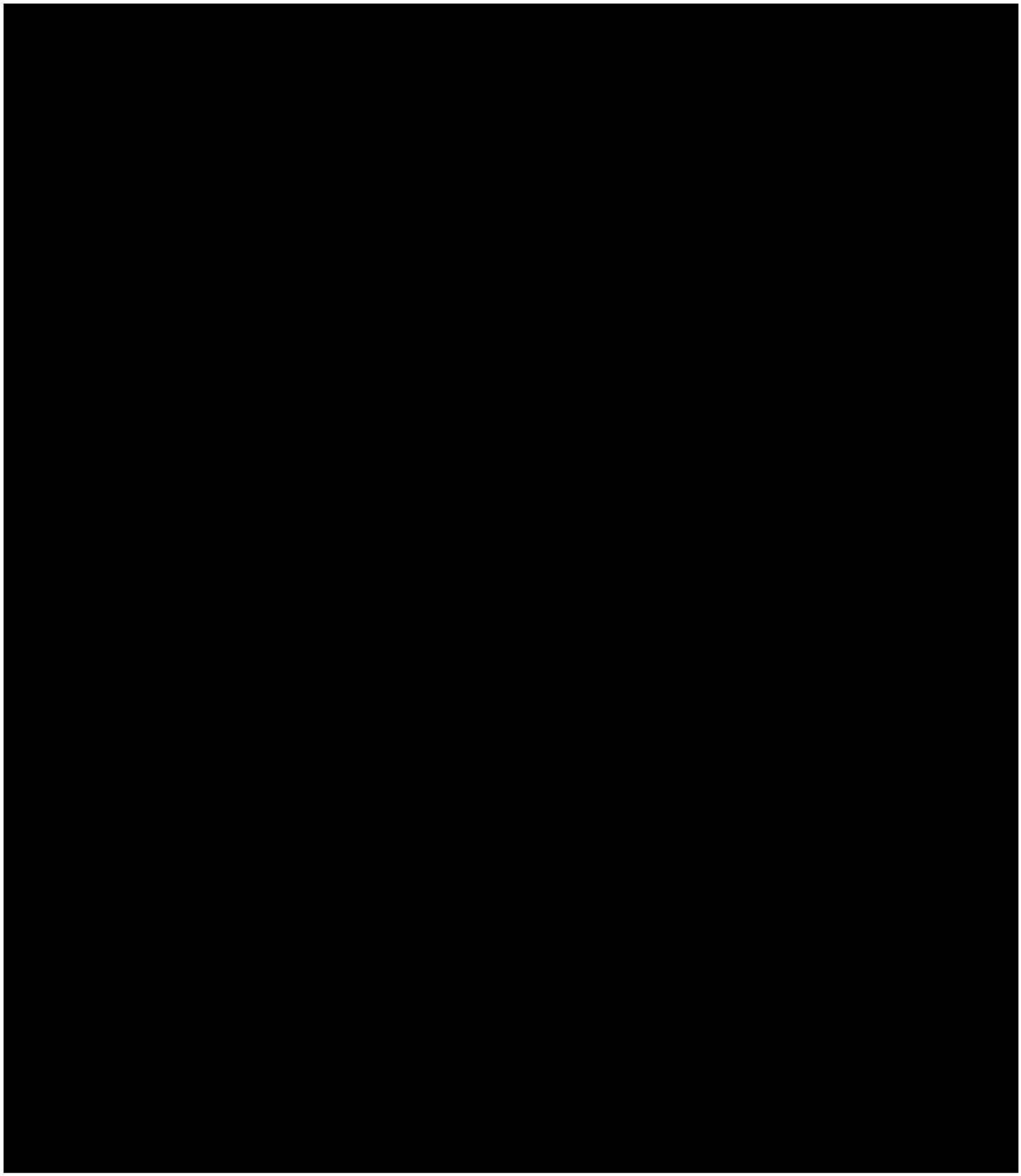
- Reasons for the early closure of a trial site by the Sponsor or Investigator may include but are not limited to:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's or designee's procedures, or GCP guidelines
  - Inadequate recruitment of subjects by the Investigator
  - Discontinuation of further IMP development
- If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and contract research organization used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

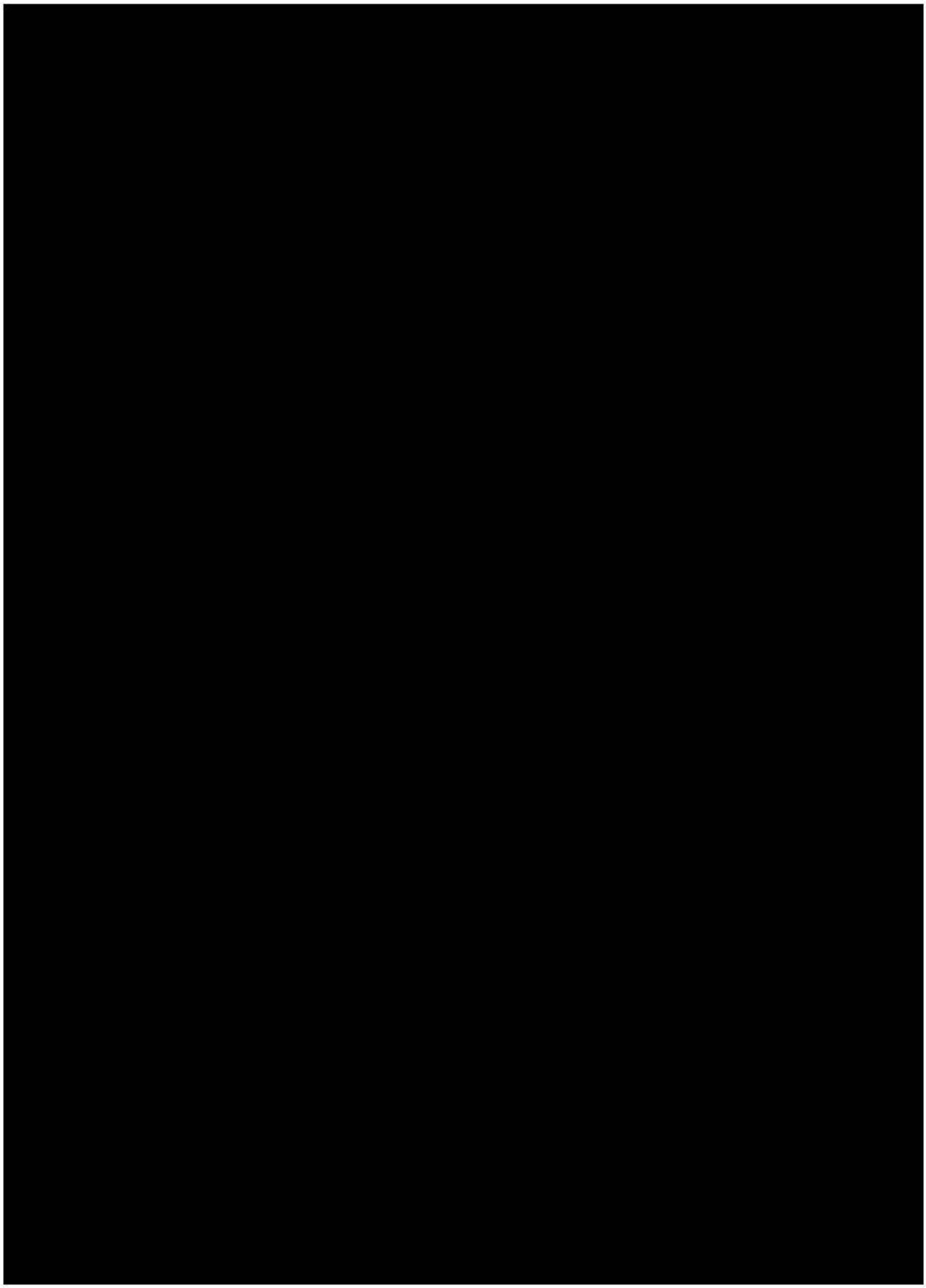
10.1.11. Publication Policy

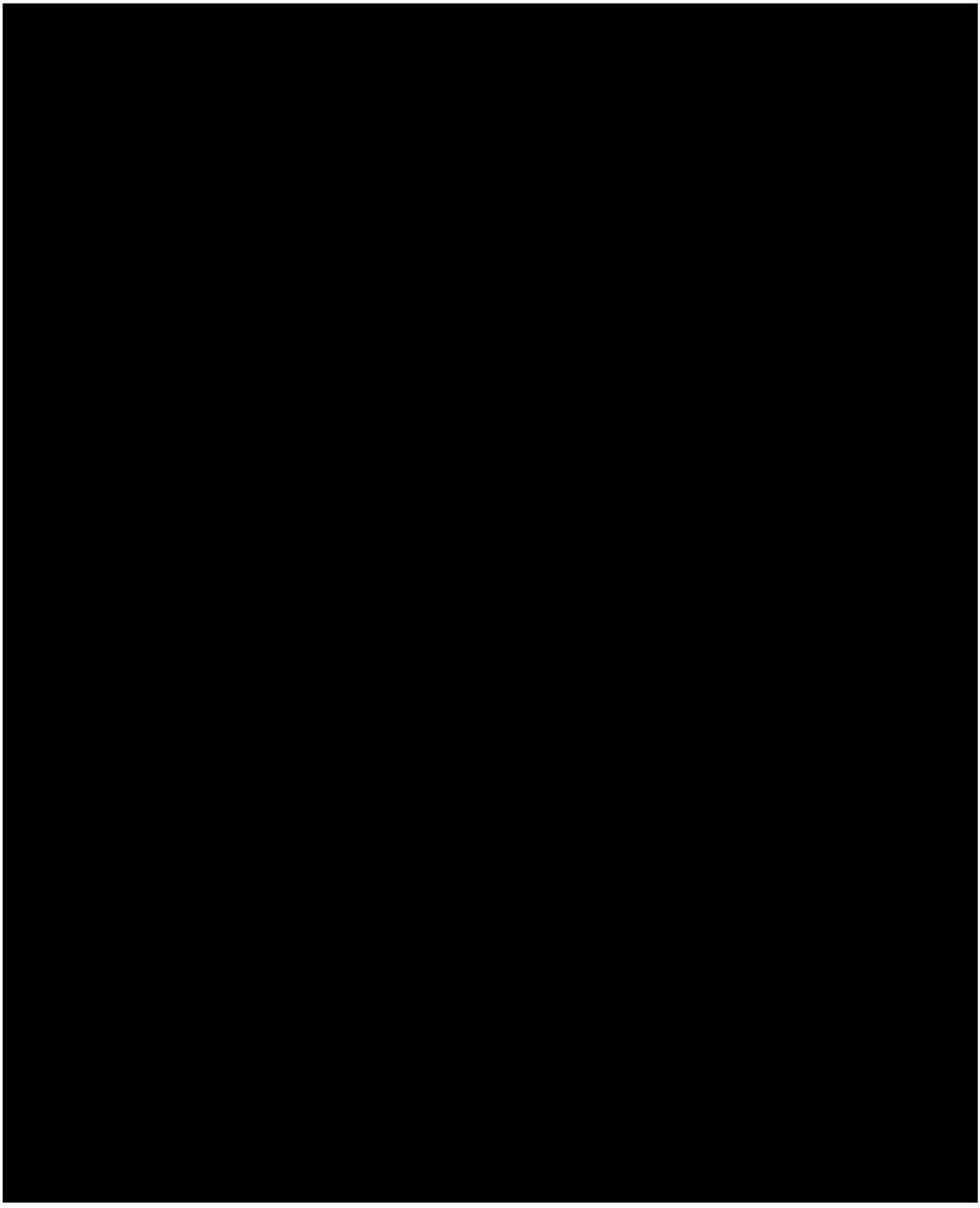
- Savara is committed to data transparency by disclosing information from its research programs through presentations at scientific congresses and publication in peer-reviewed journals. Savara adheres to the International Committee of Medical Journal Editors (ICMJE) recommendations regarding authorship.
- 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 multi-center trial may publish data subsets from their individual institution, but only after publication of the primary manuscript. A written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must be given a 30-day period to review and approve any publication manuscript prior to their submission to journals, meetings or conferences. Such a manuscript should always reference the primary publication of the entire trial.

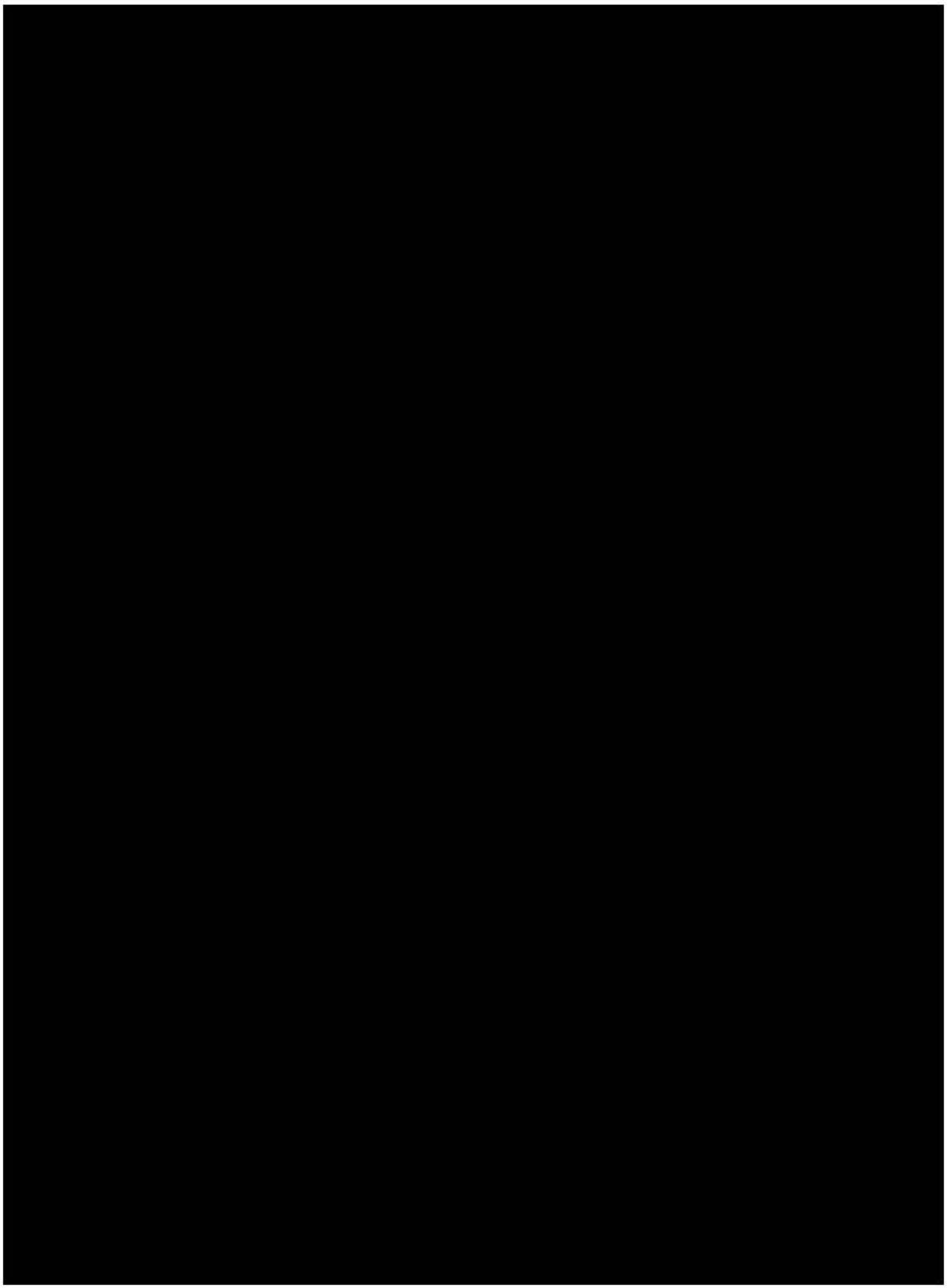
10.2. Appendix 2: Efficacy Assessments

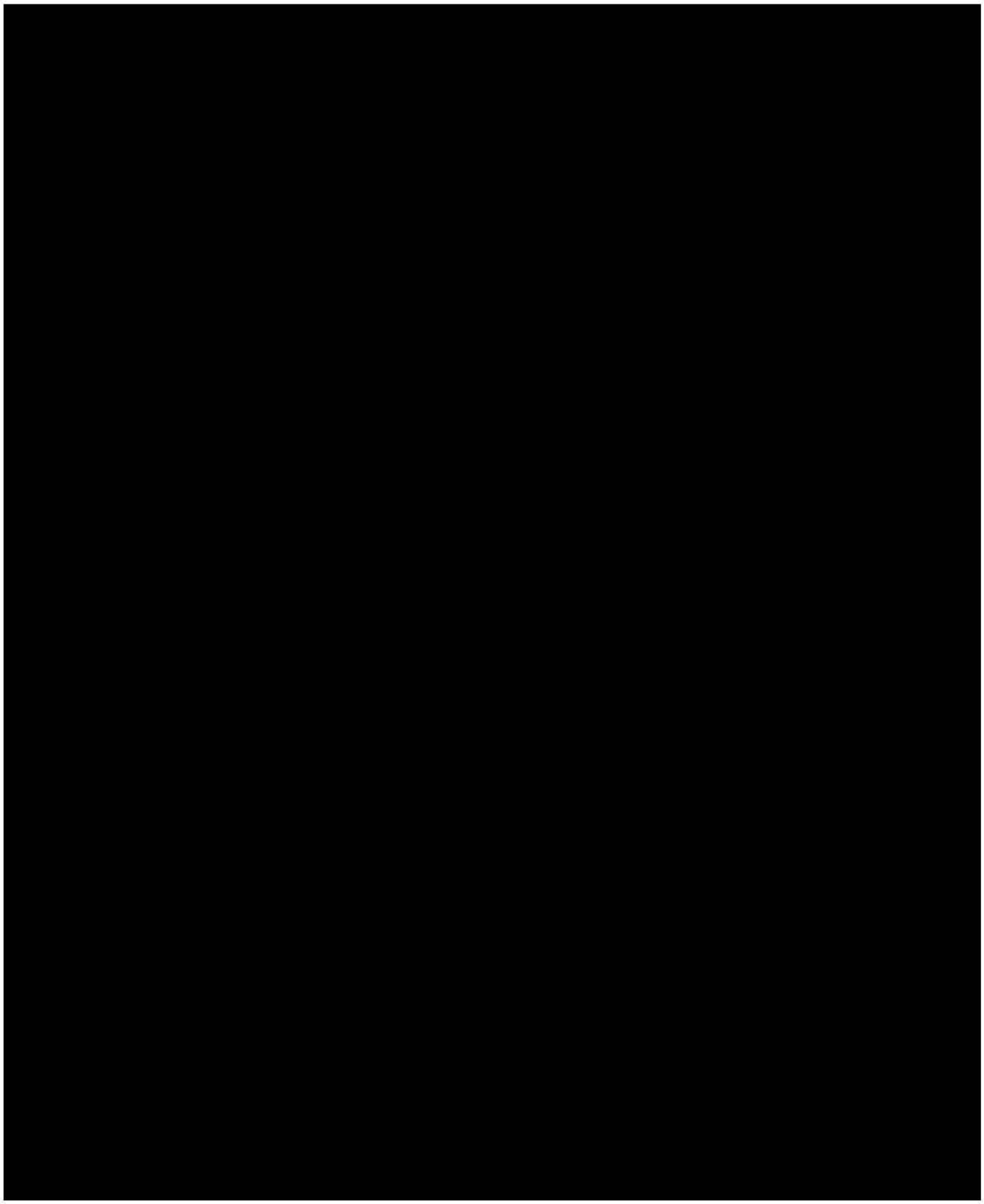
10.2.1. Sample SGRQ

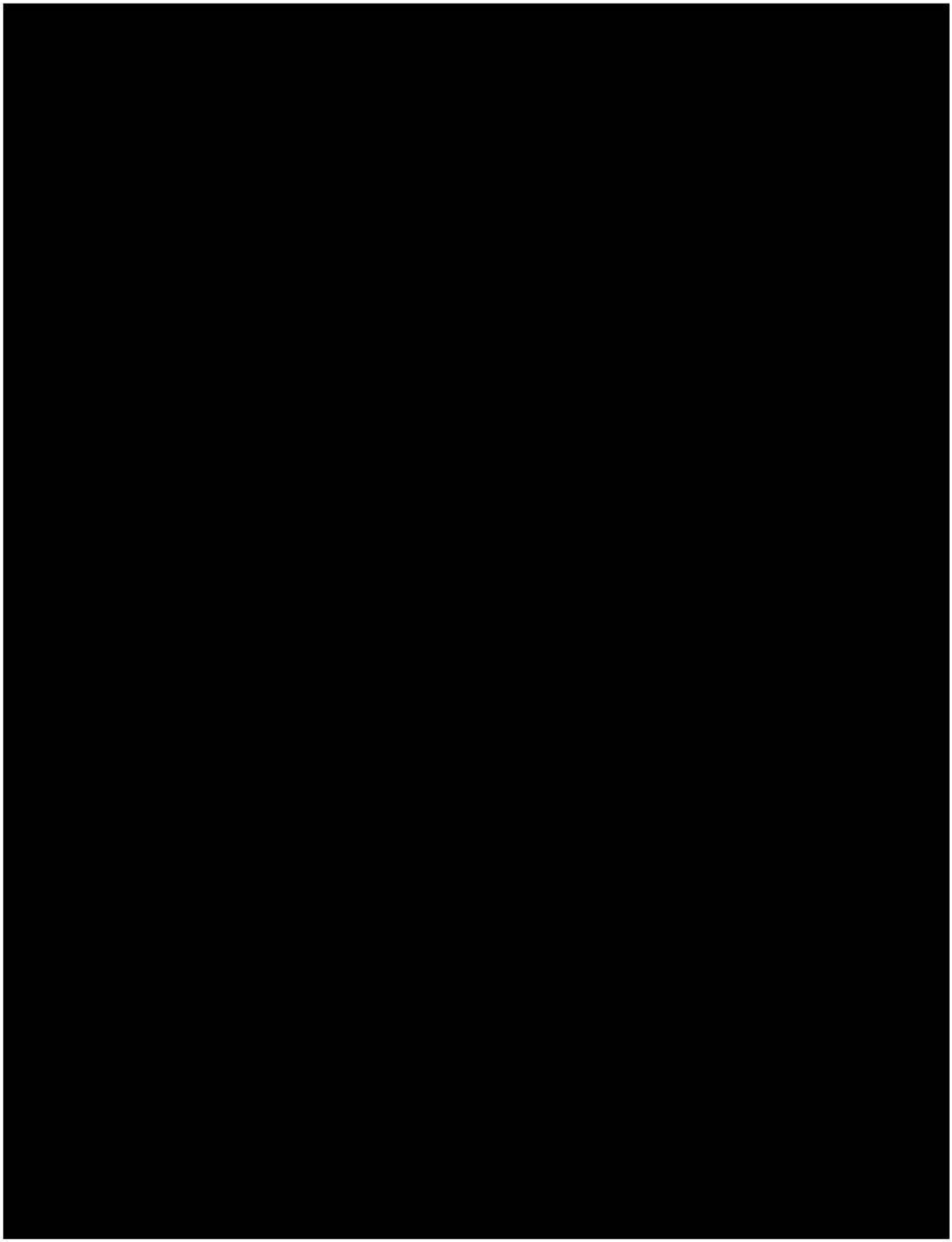












10.2.2. Exercise Test Summary Sheet

EXERCISE TEST SUMMARY SHEET

Study Number: SAV006-05	**Site Number:**	**Subject ID:**	**Visit Number:**	**ET Test Date** (DD-MMM-YYYY):

PRE-TEST INFORMATION

ET Technician Initials:	**Sex:** MALE ☐ FEMALE ☐	**Age** (yrs):	**Weight** (kg):	**Use of beta blocker within last 24 hours:** YES ☐ NO ☐ (Name / Dose): _____/_____

Disconnect supplemental oxygen, if using.			
Has the patient been off oxygen supply for at least 15 min. prior to the test?			YES ☐ NO ☐ N/A ☐
Has the subject been monitored for SpO_2 for at least 15 min. (with at least three SpO_2 measurements at 5 min intervals) prior to the test while seated and breathing room air?			YES ☐ NO ☐
Confirm SpO_2 stability > 85% and change of ≤ 2% points during the last 5-minute period of pre-test observation?			YES ☐ NO ☐
Pre-test		**SpO_2 (%)**	**Comments**
0 min			**SEATED**
5 min			**SEATED**
10 min			**SEATED**
15 min			**SEATED**
20 min	**OPTIONAL**		**SEATED**
25 min	**OPTIONAL**		**SEATED**
30 min	**OPTIONAL**		**SEATED**

EXERCISE TEST SUMMARY SHEET

Study Number: SAV006-05	Site Number:	Subject ID:	Visit Number:	ET Test Date (DD-MMM-YYYY):

EXERCISE TEST

Stage	Time from start (min:sec)	ECG print	HR (bpm)	SBP / DBP (mmHg)	Borg RPE Scale®	Dyspnea (Borg CR Scale®)	Angina Scale	SpO_2 (%)	Speed / Grade (mph/%)	Comments
Pre-exercise Phase										
Rest	-5 min	☐		__ / __						SEATED
Exercise Phase										
1	0:30								1/0	
2	1:00	☐							1.1/0.5	
3	1:30								1.2/1.0	
4	2:00	☐		__ / __					1.3/1.5	
5	2:30								1.4/2.0	
6	3:00	☐							1.5/2.5	
7	3:30								1.6/3.0	
8	4:00	☐		__ / __					1.7/3.5	
9	4:30								1.8/4.0	
10	5:00	☐							1.9/4.5	
11	5:30								2.0/5.0	
12	6:00	☐		__ / __					2.1/5.5	
13	6:30								2.2/6.0	
14	7:00	☐							2.3/6.5	
15	7:30								2.4/7.0	
16	8:00	☐		__ / __					2.5/7.5	
17	8:30								2.6/8.0	
18	9:00	☐							2.7/8.5	
19	9:30								2.8/9.0	
20	10:00	☐		__ / __					2.9/9.5	
21	10:30								3.0/10.0	
22	11:00	☐							3.1/10.5	
23	11:30								3.2/11.0	
24	12:00	☐		__ / __					3.3/11.5	
25	12:30								3.4/12.0	
26	13:00	☐							3.5/12.5	
27	13:30								3.6/13.0	
28	14:00	☐		__ / __					3.7/13.5	
29	14:30								3.8/14.0	
30	15:00	☐							3.9/14.5	
31	15:30								4.0/15.0	

EXERCISE TEST SUMMARY SHEET

Study Number: SAV006-05	**Site Number:**	**Subject ID:**	**Visit Number:**	**ET Test Date** (DD-MMM-YYYY):

Reason for stopping		
ST-segment elevation ☐	Central nervous system symptoms ☐	Technical difficulties ☐
Drop in systolic BP >10 mm Hg ☐	Signs of poor perfusion ☐	SpO_2 to <80% ☐
Moderate-to-severe angina ☐	Arrhythmia ☐	Subject request ☐ If subject request: Was primary limiting symptom: Leg Fatigue ☐ Dyspnea ☐ Other ☐ If Other, describe:
Other ☐	**Describe:**	

Recovery	**HR** (bpm)	**SBP / DBP** (mmHg)	**Borg RPE Scale®**	**Dyspnea** (Borg CR Scale®)	**Angina Scale**	**SpO_2 (%)**	**Speed / Grade** (mph/%)	**Comments**
Recovery Phase - Active Cooldown								
1 min		__ / __					1/0	**ACTIVE**
2 min							1/0	**ACTIVE**
Recovery Phase – Passive Recovery								
3 min		__ / __					--	**SEATED**
4 min							--	**SEATED**
5 min		__ / __					--	**SEATED**
6 min							--	**SEATED**

POST-TEST INFORMATION

Immediate posttest symptoms		
Chest discomfort ☐	Lightheadedness ☐	Leg fatigue ☐
Dyspnea ☐		
Other ☐	**Describe:** _____	
Were there any other abnormalities during or after the exercise test?		
YES ☐ NO ☐	**If "YES", describe:** _____	

Stopping at stage number	**Seconds completed at last stage**	**HR at termination** (bpm)	**O_2 Sat at termination** (%)

EXERCISE TEST SUMMARY SHEET

Study Number: **SAV006-05**	**Site Number:**	**Subject ID:**	**Visit Number:**	**ET Test Date** (DD-MMM-YYYY):

Approved:

_____ _____

Investigator Signature Date

10.2.3. Sample Rating of Perceived Exertion (RPE) – Borg RPE Scale®

Borg RPE Scale®

Use this scale to tell how strenuous and tiring the work feels to you. RPE stand for Ratings of Perceived (P) Exertion (E). The exertion is mainly felt as fatigue in your muscles and as breathlessness or possibly aches. When the exercise is hard it also becomes difficult to talk. It is your own feeling of exertion that is important. Don't underestimate it, but don't overestimate it either. For common exercise, such as cycling, running or walking, 11-15 is a good level. For strength and high-intensity interval training (HIIT), 15-19 is good. If you are sick follow your doctor's advice. Look at the scale and the descriptions and then assign a number. Use whatever numbers you want, even numbers between the descriptions.

6	**No exertion at all**	No muscle fatigue, breathlessness or difficulty in breathing.
7	**Extremely light**	Very, very light.
8		
9	**Very light**	Like walking slowly for a short while. Very easy to talk.
10		
11	**Light**	Like a light exercise at your own pace.
12	**Moderate**	
13	**Somewhat hard**	Fairly strenuous and breathless. Not so easy to talk.
14		
15	**Hard**	Heavy and strenuous. An upper limit for fitness training, as when running or walking fast.
16		
17	**Very hard**	Very strenuous and tiring. Very difficult to talk.
18		
19	**Extremely hard**	The most strenuous effort you have ever experienced.
20	**Maximal exertion**	Maximal heaviness.

Borg RPE Scale®
© Gunnar Borg, 1970, 1998, 2017
English

BorgPerception AB

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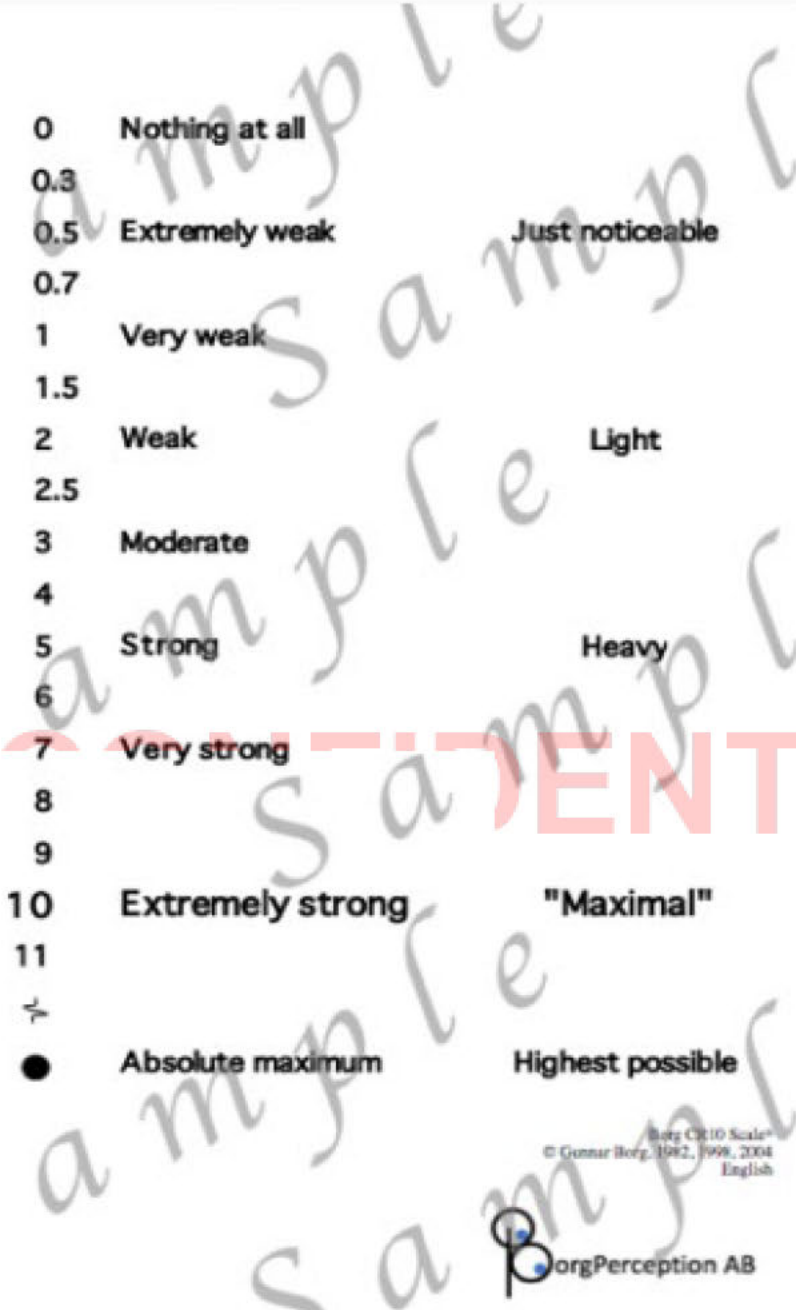
10.2.4. Sample Borg CR Scale® (CR10) for assessment of dyspnea



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10.2.5. Sample Angina Scale

1+	Onset of discomfort
2+	Moderate, bothersome
3+	Moderately severe
4+	Severe, most pain ever experienced

10.2.6. Sample Oxygen eDiary

Subjects on supplemental oxygen will complete a daily electronic diary about their oxygen use for 14 days prior to the relevant visits.

1	Have you used supplemental oxygen during the last 24 hours?	Yes	No
	If no to question 1, skip the rest of the questionnaire.		
2	Did you use oxygen at rest?	Yes	No
	If no to question 2, go to question 4		
3	What oxygen flow was used most often at rest?	____	L/min
4	Did you use oxygen during sleep?	Yes	No
	If no to question 4, go to question 6		
5	What oxygen flow was used most often during sleep?	____	L/min
6	Did you use oxygen during exertion?	Yes	No
	If no to question 6, skip the rest of the questionnaire		
7	What oxygen flow was used most often during exertion?	____	L/min
8	For how many hours did you exert and use supplemental oxygen?	____	Hrs.

10.2.7. Sample Patient's Global Impression of Severity (PGIS) and Change (PGIC) (to be completed after the SGRQ)

Please choose the response below that best describes the severity of your breathing problems.
□ None
□ Mild
□ Moderate
□ Severe
□ Very severe

Please choose the response below that best describes the overall change in your breathing problems since you started taking the study medication.
□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

Was this change in your breathing problems important for you?
□ Yes
□ No

Please choose the response below that best describes how much your breathing problems limit your daily physical activity level.
□ Not at all
□ Slightly
□ Moderately
□ Strongly
□ Very strongly

Please choose the response below that best describes the overall change in your daily physical activity level since you started taking the study medication.
□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

Was this change in your daily physical activity level important for you?
□ Yes
□ No

10.2.8. Sample Patient's Global Impression of Severity (PGIS) and Change (PGIC) (to be completed after the Exercise Test)

Please choose the response below that best describes how much your breathing problems limit your ability to exercise.

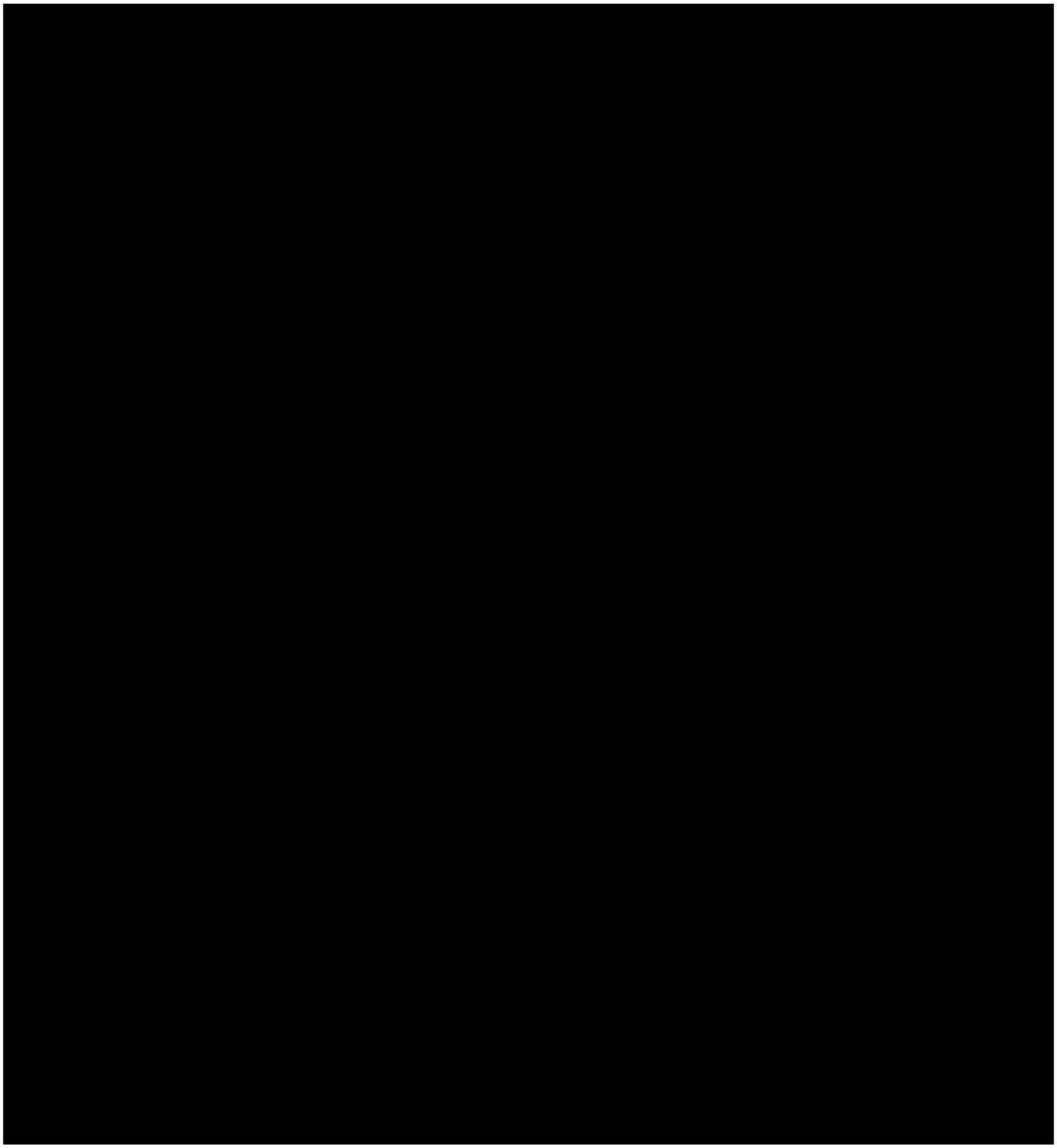
□ Not at all
□ Slightly
□ Moderately
□ Strongly
□ Very strongly

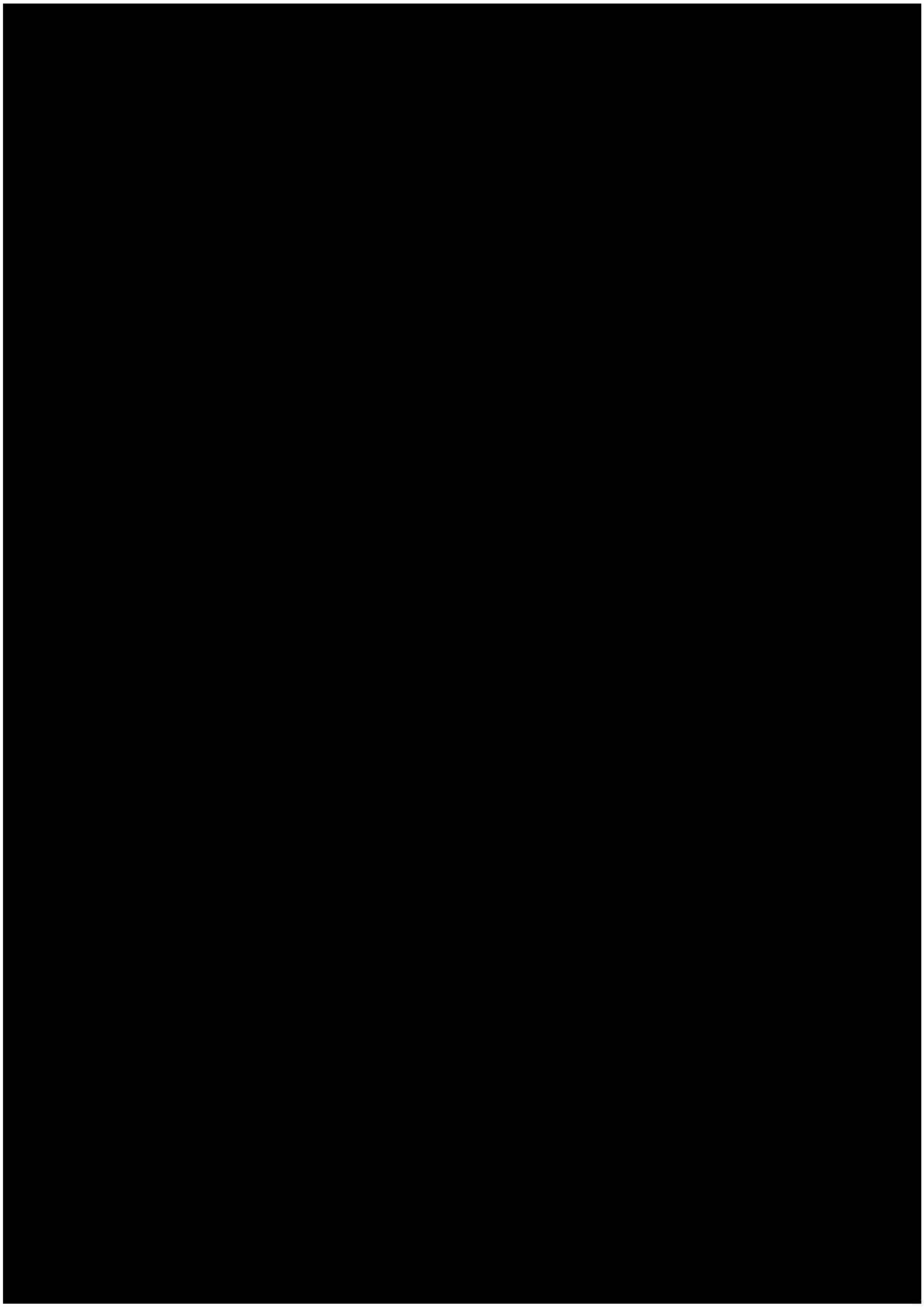
Please choose the response below that best describes the overall change in your ability to exercise since you started taking the study medication.

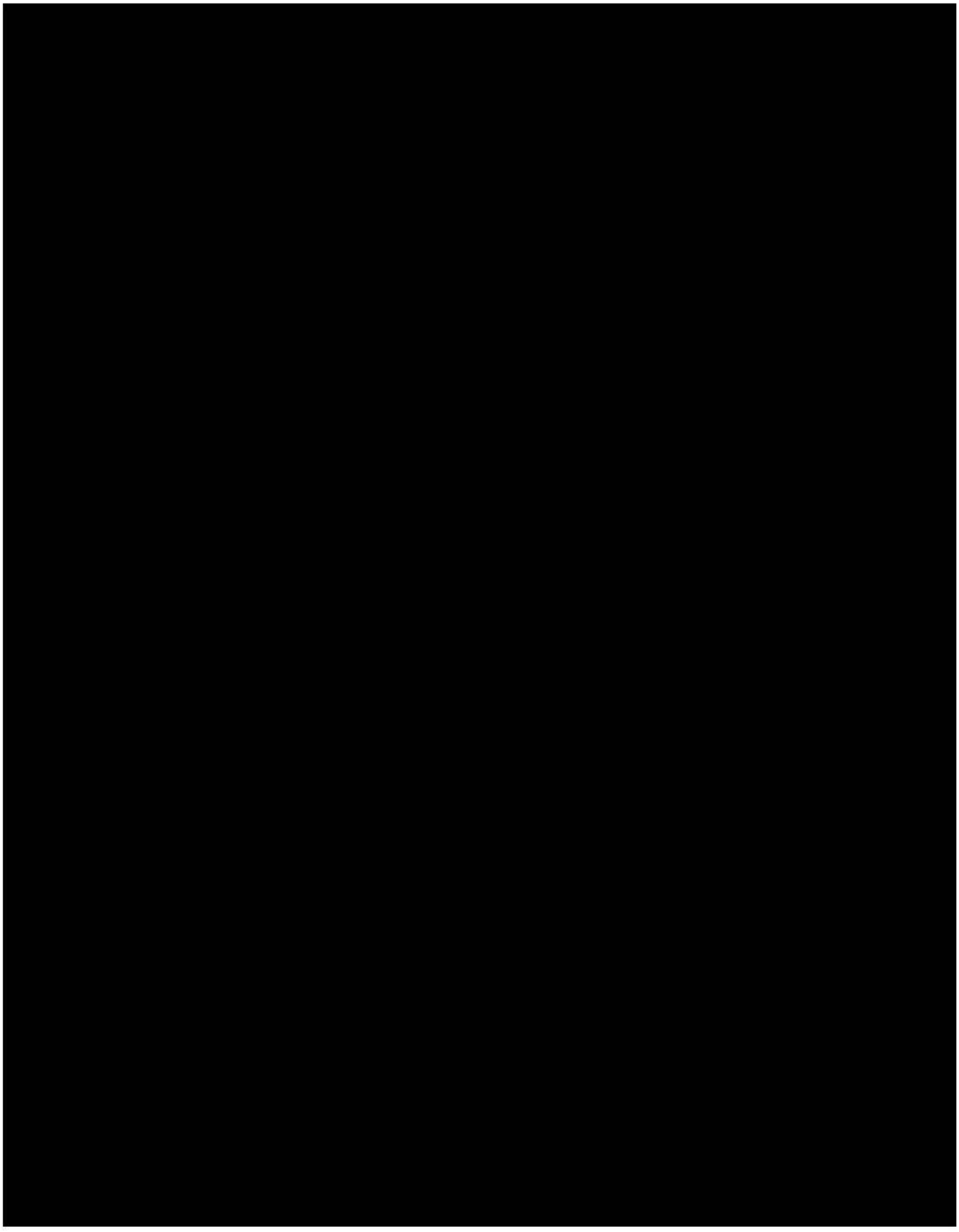
□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

Was this change in your ability to exercise important for you?

□ Yes
□ No

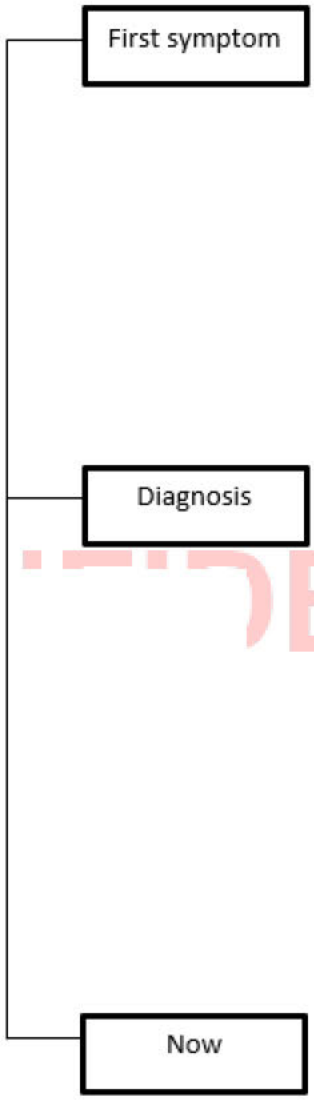






10.2.10. Sample Patient Journey

My personal timeline



10.2.11. Clinician's Global Impression of Severity (CGIS) and Change (CGIC)

CGIS

Please Provide the Investigator's Assessment of the Current Severity of aPAP (CGIS)

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

CGIC

Please Provide the Investigator's Assessment of Change from Baseline in aPAP severity (CGIC)

- ☐ Much Improved
- ☐ Somewhat Improved
- ☐ No Change
- ☐ Somewhat Worse
- ☐ Much Worse

10.3. Appendix 3: Clinical Laboratory Tests

Laboratory Assessments	Parameters
Blood hematology	• Hemoglobin • Red blood cell count and red blood cell distribution width • Hematocrit • Mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration • Platelet count • White blood cell count, and white cell differential absolute count: Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils.
Serum biochemistry	• Aspartate aminotransferase • Alanine aminotransferase • Gamma glutamyl transpeptidase • Alkaline phosphatase • Bilirubin • Urea, S-creatinine, estimated glomerular filtration rate • Potassium, sodium, calcium, chloride, phosphate • Total protein, albumin • Lactate dehydrogenase • Glucose (non-fasting)
Urinalysis	• Glucose • Nitrite • Protein • Hematuria • Microalbuminuria

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical trial subject, temporally associated with the use of IMP or other trial procedures, whether or not considered related to the IMP or the trial procedures. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP or other trial procedures.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology or biochemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator). • Worsening of the disease/disorder being studied. • Worsening of a pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after signing the ICF even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy" or "failure of expected pharmacological action" *per se* will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Events NOT Meeting the AE Definition
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

10.4.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Important medical event • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then enter all relevant AE and SAE information in the eCRF and/or SAE Report Form (additional instructions on the reporting of SAEs will be provided separately).
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor *in lieu* of completion of the AE/SAE CRF page or SAE Report Form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to one of the following categories (the most severe category should be recorded, if the intensity changes):

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities.
- An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Seriousness

- An event is defined as 'serious' when it meets at least 1 of the predefined criteria as described in the definition of an SAE (Section 10.4.2), NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.
- Causality will be assessed as either "related", "possibly related", "unlikely related" or "not related".
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

Assessment of Causality
• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always assess causality for every event before the initial transmission of SAE data. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. In case causality assessment of an AE changed over the duration of the trial, the last causality assessment will prevail. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or delegate to elucidate the outcome and causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in originally completed in eCRF or entered in the follow-up SAE Report Form. • The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the follow-up information.

10.4.4. Reporting of SAEs

SAE Reporting to the Sponsor
• The primary mechanism for reporting an SAE will be via entry to the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a trial subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form. • Contacts for SAE reporting will be provided to the sites and can be found in the Investigator TMF.

10.5. Appendix 5: Contact Information for Medical Monitor, Technical Facilities and Central Laboratories

Global Medical Monitor

[redacted]

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

Reference Laboratory (Anti-GM-CSF Analysis)
Name: Bioagilytix
Address: Lademannbogen 10, 22339 Hamburg, Germany
Phone: +49 40 5267790

CRO (Submissions, IMP supply, Monitoring, Data Management, Programming, Statistics and Pharmacovigilance)
Name: Parexel International (IRL) Limited
Address: One Kilmainham Square, Inchicore Rd., Dublin 8, Ireland
Phone: + 353 1473 9500

Central ECG, Lung Function Test, ePRO and Imaging
Name: Clario
Address: Sieboldstrasse 3, 97230 Estenfeld, Germany
Phone: +49 9305 720 60

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

10.6. Appendix 6: Signature Page

This Clinical Trial Protocol is approved by:

SPONSOR OPERATIONS LEAD Signature: Date: Refer to electronic signature and date. …… [redacted]
SPONSOR CLINICAL LEAD Signature: Date: Refer to electronic signature and date. …… [redacted]
INTERNATIONAL COORDINATING INVESTIGATOR Signature: Date: Refer to next page …… [redacted]

10.6. Appendix 6: Signature Page

This Clinical Trial Protocol is approved by:

SPONSOR OPERATIONS LEAD Signature: Date: Refer to electronic signature and date. …… [redacted]
SPONSOR CLINICAL LEAD Signature: Date: Refer to electronic signature and date. …… [redacted]
INTERNATIONAL COORDINATING INVESTIGATOR [redacted]

10.7. Appendix 7: Abbreviations

- 6MWD 6-minute walk distance
- 6MWT 6-minute walk test
- A-aDO_2 Alveolar-arterial oxygen difference
- ADR Adverse drug reaction
- AE Adverse event
- AESI Adverse event of special interest
- Anti-GM-CSF Antibodies to granulocyte macrophage colony stimulating factor
- aPAP Autoimmune pulmonary alveolar proteinosis
- ATS American Thoracic Society
- BAL Bronchoalveolar lavage
- CEA Carcinoembryonic antigen
- CGIC Clinician's Global Impression of Change
- CGIS Clinician's Global Impression of Severity
- CFR Code of Federal Regulations
- CI Confidence interval
- COPD Chronic obstructive pulmonary disease
- CRA Clinical research associate
- CT Computed tomography
- CTIS Clinical Trial Information System
- CTR Clinical Trial Report
- CYFRA 21-1 Cytokeratin 19 fragment
- DLCO Diffusing capacity of the lungs for carbon monoxide
- DMC Data monitoring committee
- DSS Disease severity score
- EC Exercise capacity
- ECG Electrocardiogram
- eCRF Electronic case report form
- EDC Electronic Data Capture
- EQ-5D-5L EuroQoL 5 Dimensions, 5 Levels
- ERS European Respiratory Society

- FAS Full analysis set
- FEV_1 Forced expiratory volume in one second
- FDA Food and Drug Administration
- FiO_2 Fraction of inspired oxygen
- FRIEND Fitness Registry and the Importance of Exercise National Database
- FVC Forced vital capacity
- GGO Ground glass opacity
- GM-CSF Granulocyte macrophage colony stimulating factor
- Hb Hemoglobin
- Hct Hematocrit
- HRCT High resolution computed tomography
- IB Investigator's Brochure
- ICF Informed Consent Form
- ICH The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- IEC Independent Ethics Committee
- IMP Investigational medicinal product
- IRB Institutional Review Board
- IRT Interactive Response Technology
- KL-6 Krebs von den Lungen-6
- LDH Lactate dehydrogenase
- Lsmean Least squares mean
- MedDRA Medical Dictionary for Regulatory Activities
- MET Metabolic equivalent
- MOL Molgramostim 300 µg nebulizer solution
- MOL-INT Molgramostim 300 µg nebulizer solution intermittent treatment
- MOL-OD Molgramostim 300 µg nebulizer solution once-daily treatment
- PaO_2 Arterial partial pressure of oxygen
- PAP Pulmonary alveolar proteinosis
- PBO Placebo (treatment group)
- PGIC Patient's Global Impression of Change

- PGIS Patient's Global Impression of Severity
- PPS Per-protocol set
- PT Preferred term
- QTcF QT interval corrected by Fridericia
- rhGM-CSF Recombinant human granulocyte macrophage colony stimulating factor
- RPE Rating of Perceived Effort
- SAE Serious adverse event
- SAP Statistical analysis plan
- SAS Safety analysis set
- SD Standard deviation
- SGRQ Saint George's Respiratory Questionnaire
- SoA Schedule of Activities
- SOC System organ class
- SpO_2 Oxygen saturation
- SUSAR Suspected unexpected serious adverse reaction
- TMF Trial master file
- US United States
- VAS Visual Analogue Scale
- VC Vital capacity
- VO_2 Maximum oxygen consumption
- WHO World Health Organization
- WLL Whole lung lavage

10.8. Appendix 8: Change log

Protocol Version	Date	Changes	Rationale
1.0	22 June 2020	Not applicable (original protocol)	
2.0	17 August 2020	Amendment 1 <u>Change 1 (only applicable for Japan)</u> Promotion of the exploratory efficacy endpoint 'Change in A-aDO_2 from baseline to Week 24' to a secondary endpoint. This change caused updates to the following sections: • Section 1.1, Synopsis • Section 3, OBJECTIVES AND ENDPOINTS • Section 4.2.3.2, Secondary Endpoints • Section 9.3.2., Estimands for the Secondary Efficacy Endpoints • Section 9.5.1, General Considerations • Section 9.5.6, Secondary Endpoints <u>Change 2 (applicable for all countries)</u> Addition of an exclusion criterion ('Known active infection [viral, bacterial, fungal. Or mycobacterial] that may affect the efficacy evaluation in the trial'). This change caused updates to the following section: • Section 5.2, Exclusion Criteria	The protocol was amended on 17 August 2020 due to two requests by the Pharmaceutical and Medical Devices Agency (PMDA), Japan, during pre-trial consultation. Amendment 1 is considered substantial.
3.0	08 September 2020	Amendment 2 Adding more frequent full physical examination, and symptom-oriented or	The protocol was amended on 08 September 2020 due to requests from European Regulatory Authorities

Protocol Version	Date	Changes	Rationale
		brief physical examination at interim visits. This change caused updates to the following sections: 1.3 Schedule of Activities 8.3.2. Physical Examination Adding a definition of postmenopausal and women of child-bearing potential. This change caused updates to the following sections: Section 5.1. Inclusion Criteria Adding an exclusion criterion for women who are pregnant, planning to become pregnant during the trial, or breastfeeding. This change caused updates to the following sections: Section 2.3.1 Risk Assessment Section 5.2, Exclusion Criteria Adding a definition of postmenopausal and women of child-bearing potential. This change caused updates to the following section: Section 5.1. Inclusion Criteria Adding a definition of postmenopausal and women of child-bearing potential. Clarifying that subjects who cannot conduct an assessment because their condition worsened so that they cannot discontinue supplemental oxygen will stay in the trial and conduct all other assessments according to the protocol This change caused updates to the following section: Section 6.5.4 Oxygen Supplementation	during a Voluntary Harmonization Procedure. Amendment 2 is considered substantial.

Protocol Version	Date	Changes	Rationale
		Clarifying that in case of safety concerns the subject may discontinue the IMP if deemed necessary by the investigator. This change caused updates to the following section: Section 8 Trial Assessments and Procedures Specifying the timeframes for reporting of SUSARs (7 versus 15 days) This change caused updates to the following section: 8.4.4. Regulatory Reporting Requirements for SAEs	
4.0 Revised	25 March 2021	Amendment 3 The changes specified in the 'Rationale' column caused updates to the following protocol sections: 1.1. Synopsis 1.2. Schema 1.3. Schedule of Activities (SoA) 10. Objectives and endpoints 4.1 Overall design 4.2.1. Choice of Overall Trial Design 4.2.3.2. Secondary Endpoints 4.4. End of Trial Definition 5.2. Exclusion Criteria 6.2.2. Administration 6.2.3. Storage 6.3.1. Double-blind Treatment Period 6.5.3. Rescue Treatment 8.2.1. Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)	To address recommendations from the FDA, the protocol was amended to: • Add PK sampling pre-dose and 2 hours post-dose at baseline, Week 4, Week 24 and Week 48. • Convert Week 98 telephone follow-up visit to a Week 100 on-site visit to collect samples for anti-GM-CSF antibody analysis. • Change scope of biobank sample to cover analyses to support efficacy or safety. • Revise the secondary endpoint hierarchy to include 48-week endpoints for all countries except Japan and South Korea. • Replace the interim analysis with a blinded sample size re-assessment and an unblinded safety review. To address requirements of the South Korean competent authority, the protocol was amended to: • Upgrade (A-a)DO_2 to a secondary endpoint for South

Protocol Version	Date	Changes	Rationale
		8.2.3. Exercise Capacity (EC) 8.2.4. Whole Lung Lavage (WLL) 8.2.8. Biobank 8.2.13. Exit Interviews 8.3.5. Pregnancy Test 8.3.6. Anti-GM-CSF Antibodies 8.4.1. Time Period and Frequency for Collecting AE and SAE Information 8.6. Pharmacokinetics 9. Statistical Considerations 9.2. Sample Size Determination 9.3. Trial Estimands 9.3.2. Estimands for the Secondary Efficacy Endpoints (all subsections) 9.5. Statistical Analyses (all subsections) 9.6. Interim Analyses 9.7. Data Monitoring Committee 10.1.5. Committees Structure 10.1.7. Data Quality Assurance 10.2.2. Exercise Test Summary Sheet 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 10.5. Appendix 5: Contact Information for Medical Monitor, Technical Facilities and Central Laboratories 10.6. Appendix 6: Signature Page	Korea (as already done for Japan). • Revise two exclusion criteria to mention specific pulmonary conditions that may confound analysis of the primary endpoint. To address requirements of the French IEC, the protocol was amended to: • Add an exclusion criterion for vulnerable subjects. To address requirements of the German IEC, the protocol was amended to: • Elaborate on remote access to patient information if needed during the COVID-19 pandemic. To improve feasibility and oversight of the exercise treadmill test (ETT), the protocol was amended to: • Update the description of the ETT and the exercise summary sheet. To provide additional data on performance of critical tasks and improve compliance, the protocol was amended to: • Add mandatory repeat nebulizer training assessment at Week 4. To reflect changes in trial operational set-up, the protocol was amended to: • Update the list of CROs and align procedures accordingly. In addition: • Minor changes to data collection were added. • Minor edits were made throughout for clarity and consistency. Amendment 3 is considered substantial.
5.0	June 28, 2021	1.3 Schedule of Activities	

Protocol Version	Date	Changes	Rationale
		• Prior and concomitant therapy added to unscheduled visits • Vitals and body weight added to all visits • Exercise Treadmill Test added to early withdrawal • Oxygen diary card added to all visits • Baseline Exercise Treadmill Test and HRCT performed up to 3-week after Screening Visit 2, but prior to baseline visit. At other time points, allow 7 days flexibility. • Blood sampling for GM-CSF gives a window of 30 minutes • Return ancillaries added to last visit and early withdrawal 2.2 Background, 2.2.1 aPAP • Deleted words that state the whole lung lavage are done under general anesthesia, can be done in intensive care units, and washes out fluid from alveoli 2.2.2 Benefit Assessment • Removed the work "curative' from the statement that no evidence-based treatment exists for aPAP 5.1 Inclusion Criteria • The requirement of DLCO to be 70% or lower at the Screening visit and Baseline visit clarified by adding the qualifier "first" to the Screening visit	• These are relevant information to obtain at all visits • Vitals and body weights are relevant information to obtain • Collect this information on patients withdrawing from the study early • Collect and record this information • Exercise Treadmill Test and HRCT are time consuming and may be done at different facilities. The change allows for in scheduling and would not impact trial design. • No window was previously specified • Not specified previously • Such details are redundant and not necessary to make the point that whole lung lavage is an invasive and difficult procedure • The word "curative" may imply that other forms of medical treatment may exist for aPAP, which is not the case • There are two Screening visits in the study, at -6 weeks (first screening visit) and – 3 weeks (second screening visit). Adding the word "first" clarifies that DLCO 70% or lower is necessary for the first screening visit. The second screening visit is to check for DLCO variability

Protocol Version	Date	Changes	Rationale
			to exclude patients with a variability of 15% or higher.
		• Remove the requirement that patients enrolled in the study have functional impairment in the treadmill exercise test (defined as peak METS of 8 or lower)	• The exercise test will be performed, and the peak METS will be used as the baseline value, but not be used as an eligibility requirement. While it is reasonable to enroll patients who are functionally impaired, there is no previous data what that impairment number would be in METS in patients with aPAP. The value of 8 was chosen arbitrarily partly using information of oxygen saturation of aPAP patients. Enrolling patients at any METS would not materially change the study, because on treatment patients can still show improvement form a baseline METS number to a higher number. Changing a criterion on a secondary endpoint is also not materially critical. This change would not impact the conduct of the study and the planned data analysis. The change was decided before any patient was randomized.
		5.2 Exclusion criteria 20. *For France only: including as further defined by French Health Code* ***articles L1121-6, L1121-8, and L1121-8-1***.	Address the requirement for France specific language aligned to the global protocol
		6.2.2 Administration (of IMP) • The word "approximately" inserted to the statement that the nebulizer handset will be replaced every 4 weeks, and to the statement that subjects will administer the trial treatment at the same time of the day.	• The change of nebulizer handset periodicity, and the timing of trial treatment administration is qualified by the word "approximately" to clarify that some reasonable variability around these time points can be accepted.

Protocol Version	Date	Changes	Rationale
		5.3.1 Double-Blind Treatment Period • Added words "are intended to" and "approximately" to stratification based on DLCO threshold and region • Added Australia to the region of Asia.	• Stratification numbers are intended and not absolute because it is not possible to predict screen failure rates and dropout rates. Wording added to clarify these points. • Australia added as a new country and Australia will be added as a country to the region Asia for stratification.
		6.5.2 Concomitant Therapy • A sentence added to state that the disallowed therapies start at the time of signing informed consent.	• Clarifying langue added to make it clear the disallowed therapy monitoring starts at the time of signing informed consen
		6.5.3 Rescue Treatment • Wording changed around whole lung lavage procedure to make the sentence read better	• Minor change in writing style
		8.2.6 Supplemental Oxygen Use • Duplicate use of the word PaO2 removed	• Minor change in writing style
		9.2 Sample Size Determination • A word "delegate" added as an alternate to Sponsor to specificity who will conduct blinded sample size re-assessment after 80 subjects have completed the Week 24 visit.	• Adding the word "delegate" clarifies that the blinded sample size re-assessment will be conducted either by the Sponsor or a delegate, such as Parexel as the CRO for the trial.
		9.7 Data Monitoring Committee	

Protocol Version	Date	Changes	Rationale
		• Specific reference to "The Development Safety Team" removed to the statemnt that safety evaluation will also be performed by the Sponsor.	• Safety of the study subjects will be reviewed by the Data Monitoring Committee and also by the Sponsor of the trial. Specific reference to a specific Development Safety Team is not necessary and removed.
		Overall Design (page 11) • Corresponding changes made to the Overall Design to capture changes that are also captured in the Overall Design Section.	• Relevant sections are on subject stratification based on DLCO % predicted and on region • And adding Australia as a new country and to the region of Asia. • Clarification on aPAP diagnosis criteria to ensure consistency with 5.1 inclusion criteria
6.0	August 5, 2021	1.3 Schedule of Activities • Removal of 'X' for 'Resting vital signs and body weight' and 'Oxygen diary' at Week 52, Visit 125.7 Exclusion Criteria 5.7 Exclusion Criteria • Removal of reference to French Health Codes in Exclusion Criterion 18 • Removal of Exclusion Criterion 19	'X' was inadvertently added to these assessments due to typographical error (Visit 12 is conducted via telephone) Address request during Virtual Harmonization Process (VHP) review to remove these references, and to ensure identical protocol wording in all global regions outside of France.
7.0	October 6, 2022	5.4 Screen Failures • Removal of sentence that limited re-screening of subjects to situations where a required screening assessment fails due to a non-aPAP related, temporary problem • Clarification that re-screening of a particular subject should be discussed with the Medical Monitor	Patients whose aPAP may have become more severe since initially screen failing could be considered appropriate for re-screening (such as if screen fail reason was DLCO >70% predicted). The study Medical Monitor is the appropriate person with whom to discuss potential re-screenings.

Protocol Version	Date	Changes	Rationale
8.0	January 25, 2023	1.1 Synopsis – Overall Design • 2nd bullet – See section 6.3.1 below • 4th bullet – Removal of reference to demonstrating functional impairment in exercise treadmill test 6.3.1 Double-blind Treatment Period • Removal of sentence that stipulated a randomization cap by stratum based on DLCO 9.2 Sample Size Determination • Removal of reference to a cap on recruitment 10.5 Contact Information • Update to name of global medical monitor • Change of vendor name from ERT to Clario	Reference to functional impairment in section 1.1 should have been deleted in version 5.0, where this requirement was removed (see p. 119 above). It was not removed at that time due to an editorial oversight. The remaining changes were made based on enrollment trends to date, and the fact that any cap on enrollment (whether by stratum or overall) will have no meaningful impact on the analysis of the data. Patients with DLCO <50% are fewer (currently 40% of enrolled subjects) and retention of the DLCO stratum-based enrollment cap would substantially delay completion of the trial. The global medical monitor for the study is Dr. Anthony Bohnert. ERT has changed its name to Clario.
9.0	March 20, 2023	1.3 Schedule of Assessments • Removal of ABG at Weeks 72 and 96 (Visits 14 and 16) • Addition of 48 weeks to the open-label treatment period (new Visits 17-20) • Change of safety follow-up from Visit 17 (Week 100) to Visit 21 (Week 148) 1.3 Schedule of Assessments and throughout the document • Change all reference to duration of open-label treatment period from 48 weeks to 96 weeks 10.2.2 Exercise Treadmill Test Summary Sheet • Replacement of version 1.0 with version 2.0	ABG and respiration rate are not of significant clinical or scientific interest during the open-label treatment period, and reduces burden on the subject. Open-label treatment with molgramostim was increased by 48 weeks to obtain additional long-term safety and to assess the durability of effect. Exercise Treadmill Test Summary Sheet was up-versioned in July 2022.

Protocol Version	Date	Changes	Rationale
9.1	November 21, 2023	1.3.2 Open-label Treatment Period • Addition of 'X' at Week 148 (Visit 21) for "Resting vital signs and body weight" • Addition of footnote 'b' next to the 'X' at Week 148 (Visit 21) for "Blood sample for biomarkers, anti-GM-CSF antibodies and, optionally, biobank" 5.2 Exclusion Criteria • Text added to Criterion no. 18, which is applicable to sites in France only • Criterion no. 19 added, which is applicable to sites in France only 8.3.1 Electrocardiograms • Clarification of wording to state that three unique ECG assessments are to be performed at the indicated visits 10.8 Appendix 8: Change log • Deletion of wording "and resting respiration rate," which was erroneously included in the change log for version 9.0	The omission of this 'X' in version 9.0 was inadvertent; the Case Report Forms prompt for the collection of these data at all visits. Simply a clarification to align with version 8.0, where this footnote appears both at the top of the Week 148 ("Safety FU") column and next to the 'X.' These additions allow for a single global protocol (previously there was a separate version specific to France). The instructions as previously worded could have been misconstrued as requiring only a single ECG assessment to be uploaded three times. Resting respiration rate is assessed at Weeks 72 and 96, as noted in the Schedule of Activities (Section 1.3), and the Case Report Forms prompt for the collection of these data at all visits.
10.0	October 9, 2024	Title page • Addition of EU Clinical Trial number Synopsis – Objectives and Endpoints and 3 Objectives and Endpoints • Addition of "Change in GGO from baseline to Week 144 and from Week 24 to Week 144" as long-term exploratory endpoint 1.3.2 Schedule of Assessments	To comply with requirements in the Clinical Trial Regulation in the EU. To evaluate the data obtained from the extra HRCT scan.

Protocol Version	Date	Changes	Rationale
		• Addition of an HRCT scan to the Week 144 visit (Visit 20).	To obtain additional information regarding long-term impact of molgramostim on HRCT appearance in aPAP
		• Change from mandatory to optional assessment at unscheduled visits for 'prior and concomitant therapy', 'resting vital signs and body weight', and 'adverse events'	To clarify that all assessments at unscheduled visits are performed at the discretion of the investigator
		• Clarification that the safety follow-up visit (Week 148) must be performed 3-5 weeks after the Week 144 visit.	The safety follow-up assessments should be performed approximately 4 weeks after the last dose of IMP.
		2.3.1 Risk Assessment	
		• The number of mandated HRCT was updated from 2 to 3.	See rationale for additional HRCT scan above.
		6.2.2 Administration	
		• Updates of text regarding how to report technical complaints related to the drug product or device.	To align information in the Investigator Drug Manual with the protocol.
		8.2.5 High Resolution Computed Tomography (HRCT)	
		• Added statement that the independent GGO readers will not be blinded to subjects' treatment assignment and sequence of the assessed scans at new Week 144 HRCT scan.	Clarification of the procedure.
		8.3.1 Electrocardiograms	
		• Clarification that after Week 48 (and at the time of implementation of protocol version 10.0), only a single 12-lead ECG assessment will be obtained.	To clarify that 3 unique ECG assessments are only needed during the double-blind 48-week period.
		8.4.4 Regulatory Reporting Requirements for AEs and SAEs	
		• Updates of text regarding reporting requirements in the EU for SUSARs.	To comply with requirements in the Clinical Trial Regulation in the EU.

Protocol Version	Date	Changes	Rationale
		10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations • Updates of text regarding regulatory and ethical considerations, protocol compliance, data protection, and data quality assurance. Whole document • Minor edits, clarifications, and updates have been made throughout the document.	To comply with requirements in the Clinical Trial Regulation in the EU. To enhance clarity and correct non-substantial errors.

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