SAV006-03

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

NCT03482752

Statistical Analysis Plan

Version 3.0

21 January 2021

Statistical Analysis Plan

Molgramostim Nebuliser Solution
SAV006-03
An open-label, non-controlled, multi centre clinical trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis patients

IMPALA Extension trial

A Phase III Trial

Author: Helle Hartvig
Princial BioStatistician
BioStata ApS

Signature page

The signatures below confirm that the signees have read, understood and approved of the contents of the present statistical analysis plan.

Signature & Date
DocuSigned by:  Signer Name: Helle Væver Hartvig Signing Reason: I approve this document Signing Time: 21-Jan-2021 | 11:16 CET D9BBD6AF35E64FFDAF5D684AD07FBEDC Helle Hartvig, BioStata ApS, Trial statistician
DocuSigned by:  Signer Name: Maj Dinesen Signing Reason: I approve this document Signing Time: 21-Jan-2021 | 03:21 PST [illegible] Maj Dinesen, Savara ApS, Director Clinical Development

Table of Contents

Change Log

Version number	Date	Change
1.0	28NOV2019	Original version
2.0	27JAN2020	Analysis set for listings updated to all subjects in section 5.1 and section 12. SAS program inserted as part of section 7.2.5. List of output for safety update has been updated in section 8.2. QTcF has been added to the list of endpoints in section 8.1.5.
3.0	21JAN2021	Description of early termination added in section 3.2. Section 5.2 about issues caused by the COVID-19 pandemic has been added including 5 new outputs. Listing of screen failures and the definition of a subject being terminated early have been added to section 5.3. A table of last visit attended before closure is added in section 6.1. Furthermore, relative exposure has been defined and two outputs have been added to the same section. A table and a listing of non-serious adverse events have been added in section 7.1. Furthermore, tables of adverse events and non-serious adverse events by preferred term with frequency ≥ 5% have been added to this section. Responder endpoints and their analyses have been deleted from section 7.2.3 Summary of evaluation of vital signs has been removed from section 8.1.4 Summary of evaluation of ECG has been removed from section 8.1.5

1 List of Abbreviations

ADR	*Adverse Drug Reaction*
ALT	*Alanine Aminotransferase*
AST	*Aspartate Aminotransferase*
AE	*Adverse Event*
aPAP	*autoimmune Pulmonary Alveolar Proteinosis*
ATC	*Anatomical Therapeutic Chemical Classification System*
BMI	*Body Mass Index*
CI	*Confidence Interval*
CRF	*Case Report Form*
CT	*Computed Tomography*
DBL	*Data Base Lock*
DSS	*Disease Severity Score*
ECG	*Electrocardiogram*
FAS	*Full Analysis Set*
GGT	*Gamma Glutamyl Transpeptidase*
HEENT	*head, eyes, ears, nose, and throat*
LLOQ	*Lower Level of Quantification*
MCH	*Mean cell haemoglobin*
MCV	*Mean cell volume*
MedDRA	*Medical Dictionary for Regulatory Activities*
N	*Number of Subjects*
PT	*Preferred Term*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SD	*Standard Deviation*
6MWD	*6-minute walk distance*
6MWT	*6-minute walk test*
SGRQ	*St Georges Respiratory Questionnaire*
SOC	*System Organ Class*
TEAE	*Treatment Emergent Adverse Event*
WLL	*Whole Lung Lavage*

2 Introduction

The statistical analysis plan (SAP) for the trial SAV006-03 is based on the final protocol version 5.0 24AUG2018.

The SAP describes in detail the analyses to be conducted and highlights any deviations from the analysis described in the protocol (see section 9). Deviations from methods described in this SAP, if any, will be specified in the clinical trial report.

The analysis is performed based on:

- The clinical database, which includes the electronic Case Report Forms (eCRF)

Reporting of the trial will be after the date of last subject last visit except for a safety update during the trial.

The trial is terminated early, and the final reporting will be done when all subjects have attended a final visit and the database is considered clean and locked.

3 Trial Characteristics

3.1 Trial Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

The secondary objectives are

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

3.2 Trial Design

The trial is an open-label, non-controlled, multi centre clinical trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis (aPAP) patients.

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

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

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

During the trial, Whole Lung Lavage (WLL) will be applied as rescue therapy. The criterion for performing WLL is clinical worsening of aPAP based on symptoms, reduced exercise capacity and/or findings of hypoxemia or desaturation according to the investigator's judgement. The reason(s) for conducting WLL will be documented. Subjects undergoing WLL will continue treatment with molgramostim, unless discontinuation is medically required, according to investigator's discretion.

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

Savara received advice on the MOL-PAP-002 trial results from EMA and FDA. The data demonstrated more favorable evidence of efficacy on the continuous dosing regimen. Following the advice Savara has subsequently decided to conduct an additional Phase III confirmatory trial to support future registration of the continuous dosing regimen. The SAV006-03 trial investigates an intermittent dosing regimen but considering the MOL-PAP-002 clinical trial results and the received health authority advice there will not be adequate efficacy and safety data on the intermittent dosing regimen to support a marketing authorization application for this regimen. Consequently, Savara has decided to discontinue the SAV006-03 trial and support the continued clinical investigation of the continuous dosing regimen in a new trial.

60 subjects have been enrolled in the SAV006-03 trial and enrolled subjects will be able to continue treatment until end of 2020. Of these, 55 subjects are on active treatment and 5 subjects do not receive treatment at the time of trial termination. The 5 subjects have been allowed to remain in the trial to observe development of their disease without receiving treatment.

The data from the SAV006-03 trial will be included in the ongoing safety evaluation of molgramostim nebulizer solution. The results of the SAV006-03 trial will also be included as part of a potential future marketing authorization application for use of molgramostim nebulizer solution as a potential treatment for autoimmune pulmonary alveolar proteinosis, although the intermittent dosing regimen will likely not be included as a treatment regimen under posology.

All generated data will be cleaned and assessed according to plan and will contribute to the risk-benefit profile for molgramostim. The trial will be reported according to ICH GCP requirements.

Table 1 Activities flow chart

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

Table 1: **Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**FU TC**	**Unscheduled**
	Baseline [a]	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**2 wks after trial completion**	
Time	**0**	**Week 26**	**Week 52**	**Week 78**	**Week 104**	**Week 130**	**Week 156**		
Visit Window	N/A	± 4wks	± 4 wks	± 4 wks	± 4 wks	± 4 wks	± 4 wks	+ 1 wk	
Laboratory Safety Analyses [h]	(X)	X	X	X	X	X	X		(X) [d]
AEs	X	X	X	X	X	X	X	X	X
PK samples (**Italy only**) [i]	X	X	X	X	X	X			
Medical history	X								
Dispense trial drug [j]	X	X	X	X	X	X			(X) [d]
Subject Diary Card [k]	X	X	X	X	X	X	X		
Compliance		X	X	X	X	X	X		(X) [d]
Study continuation or termination [l]		X	X	X	X	X	X		(X) [d]

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

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

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

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

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

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

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

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

[h] Haematology and clinical chemistry

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

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

[k] Diary card to collect safety information to be given to the subject and collected at the next visit. The subject will be asked to record any AEs they have experienced, enter dates for pregnancy tests taken at home (if applicable) and dates for changing of the nebuliser mouthpiece in the subject diary.

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

3.3 Subject included

No formal sample size calculation was done as this is an open-label extension trial.

Subjects with aPAP who have completed the IMPALA (MOL-PAP-002) trial will be eligible for this trial. Up to 90 subjects may be included. All subjects in need of treatment will receive inhaled molgramostim.

4 Analysis Sets

All subjects excluding screening failures will be included in the full analysis set.

All subjects with exposure within the trial will be included in the safety analysis set.

The full analysis set will be used for demographics and efficacy summaries and the safety analysis set will be used for safety summaries.

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

4.1 Protocol Deviations

Before data base lock (DBL) all protocol deviations will be evaluated and classified as minor or major. The decisions will be documented. Major protocol deviations will be listed.

5 Planned Statistical Methods

5.1 Statistical Considerations

Baseline is the value measured on visit 1 before first administration of investigational product in SAV006-003. For variables/assessments not scheduled to be performed at baseline or that are missing at baseline, the baseline value is the value from the IMPALA (MOL-PAP-002) trial measured closest to visit 1.

Numerical data will be presented using number of subjects, mean, standard deviation, median, range (minimum and maximum), as well as number of missing data (if relevant).

All summary tables for categorical variables will display counts, percentages and number of missing data (if relevant) by treatment group.

All tables will include three treatment arms based on the randomized treatment from the IMPALA trial in combination with the current treatment in the presentation of data. The treatment labels will be:

- MOL OD / MOL INT
- MOL INT / MOL INT
- PBO / MOL INT

Furthermore, all tables will include a total column.

End of trial date is set to the date of completion/discontinuation as entered in the eCRF on the end of trial page.

All listings will be made based on all subjects. They will be sorted by treatment and then subject number. A column showing which analysis sets (FAS/Safety) the subject belongs to, will be included.

Due to early closure of the trial patients will perform the measurements as described in visit 7 even though their last visit might not be visit 7.

5.2 Data Issues due to Covid-19 Pandemic

To get an overview of the impact the COVID-19 pandemic has on the trial the below output will be presented

- Listing with COVID-19 positive subjects including country and time since trial start to COVID-19 start date
- Listing of all adverse events occurring in COVID-19 positive patients including time of the adverse event relative to the COVID-19 start date
- Table with number of missed key secondary endpoints assessments due to pandemic by treatment and visit. The key secondary endpoints are (A-a)DO_2 , 6MWD, SGRQ total, DLCO (% predicted), PaO_2 and DSS
- Table with number of alternative endpoint ascertainment (telephone visits, allowed out of window visits and such) if any due to COVID-19 by treatment and visit
- Listing with all protocol deviations due to COVID-19

5.3 Subject Disposition

An overall summary table of subject disposition will be prepared with number of patients in the following categories (and sub-categories):

- Number of subjects included

- Withdrawals (potential reasons are remission of aPAP, lack of efficacy/worsening of disease, unacceptable AE, investigator decision, pregnancy, withdrawal by subject, lost to follow-up or other)
- Early terminators (patients who don't complete the trial according to protocol due to early termination of the trial).
- Completers

All information will be listed including the time (days) between completion of IMPALA and visit 1 in this trial.

A listing of screening failures will be presented including violations of inclusion and/or exclusion criteria.

5.4 Baseline Demographics

Baseline demographics consists of age, sex, race, body weight, height and BMI. Baseline demographic information will be listed and summarized using descriptive statistics. The table will also include number and percentage of patients in age groups < 65 years and ≥ 65 years.

5.5 Medical History

Medical history will be recorded at visit 1 and coded using medDRA version 21.0.

Medical history will be summarized and listed.

6 Exposure and Other Dosing Information

6.1 Exposure

Treatment with molgramostim at least once during the trial (yes/no) will be summarized by treatment.

Exposure will be summarized by treatment showing summary statistics (mean, standard deviation, median, p25, p75, minimum and maximum).

Furthermore, an output will be generated showing number of subjects with ≥ 6 months exposure, ≥ 12 months exposure, ≥ 18 months exposure etc.

Exposure will be defined as number of days from visit 1 to last kit date + 21 days or end of trial date whatever comes first.

For the safety update (see section 8.2) exposure will be calculated as number of days from visit 1 to Last kit date + 21 days or Date of last visit before cut-off for safety update whatever comes first.

Relative exposure will be defined as

Relative exposure = Exposure / number of days in trial

where exposure is defined above. Relative exposure will be summarized by treatment and listed.

Due to premature trial closure a table with last visit attended will be presented showing number of patients and percentages. For patients where the last visit was entered as visit 7, the original visit they came in for will be presented in this table based on full analysis set. A listing of visits attended will be presented.

6.2 Concomitant Medication

Concomitant medication is recorded at baseline and during trial. Concomitant medication will be coded using WHODrug version June 2017.

All concomitant medication will be summarized by ATC level 3 and preferred term. All concomitant medication will be listed.

7 Statistical Methodology for Primary and Secondary Endpoints

7.1 Analysis and Presentation of the Primary Endpoint

All adverse events (AEs) occurring after informed consent will be reported in the eCRF. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

Events judged by the investigator to be related (including all events that are judged to be possibly related or probably related) to trial treatment are defined as adverse drug reactions (ADRs).

The primary endpoints are

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Non-serious adverse events
- Adverse drug reactions (ADRs)
- Adverse events leading to treatment discontinuation

Adverse events leading to treatment discontinuation are defined as events where action taken with trial drug is marked as *Drug withdrawn in the eCRF*.

All the above adverse events will be summarized by system organ class (SOC) and preferred term (PT), and overall.

The overall summary will include AEs, serious AEs, non-serious AEs, ADRs, AEs leading to treatment discontinuation, fatal AEs and AEs by severity, AEs by action with trial treatment, AEs by outcome.

The summaries by SOC and PT will include number of events, number of subjects, proportion of subjects reporting these events, and rate of events. For each of the primary endpoints, summaries will be given by severity, relationship to trial drug, and outcome.

A summary of treatment emergent adverse events by preferred term with frequency ≥ 5% will be provided together with a summary of treatment emergent non-serious adverse events by preferred term with frequency ≥ 5%.

Patient listings corresponding to the summaries, will be provided.

In summaries of adverse events by SOC and PT the tables will be sorted first by SOC and then by PT based on the frequency in the total column.

7.2 Analysis and Presentation of the Secondary Endpoints

The secondary endpoints are

- (A-a)DO_2 during the trial
- 6 Minute Walk Distance (6MWD) during the trial
- St Georges Respiratory Questionnaire (SGRQ) total score during the trial
- Frequency of Whole Lung Lavage (WLL) during the trial
- Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) (% predicted), FEV1 (% predicted), and FVC (% predicted) during the trial
- PaO_2 and disease severity score (DSS) during the trial
- Need for oxygen supplement therapy during the trial
- Overall clinical assessment (status of aPAP and requirement for treatment since last visit)
- Number of subjects not requiring treatment for aPAP and time off treatment after discontinuation of inhaled molgramostim

7.2.1 Blood Gas Analysis

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

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

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

The Aa Gradient (A-a)DO_2 will be calculated centrally using the following formula:

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

The Aa Gradient will be summarized by visit. A corresponding mean and with confidence interval (CI) plot over time will be provided. Subjects on supplementary oxygen during blood gas sample are excluded from the relevant visits in the summary.

A corresponding listing by subject and visit will be provided including all subjects regardless of use of supplemental oxygen.

Any Aa Gradients reported in kPa will be converted to a result in mmHg, this will be done using a factor k=7.5 (kPa x 7.5=mmHg).

7.2.2 6-minute Walk Test (6MWT)

Exercise capacity will be assessed using the 6MWT to measure the 6-minute walk distance (6MWD) at the timepoints shown in Table 1.

The 6MWT should be performed twice at each visit in accordance with the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidance.

Data from both tests should be entered in the eCRF. Parameters to be recorded comprise pre and post walk dyspnea score using the Borg (CR-10) Dyspnea Score (including the difference post minus pre dyspnoea score), SpO_2 (%) at start, worst SpO_2 (%) during the walk, distance walked (m), duration of the walk (minutes and seconds), oxygen flow rate if applicable, reason for stopping early (if applicable). For each subject and each visit the results from the test with the longest distance walked will be used in the reporting of the trial.

Distance in meter, Borg score endpoints, and SpO_2 and the desaturation (first SpO_2-worst SpO_2) will be summarized by treatment and visit. Furthermore, number of subjects (N, %) who completed the test will be presented by treatment and visit.

A corresponding mean and CI plot over time as well as a corresponding listing by subject and visit will be provided for each of the endpoints.

The listing will include pre and post walk dyspnoea Borg (CR-10) score, start and worst SpO_2 (%), distance walked, duration, oxygen flow rate (L/min), use of oxygen supplementation during the test (yes/no), and stopping early (yes/no) including the reason for stopping early. Both 6MWT at each visit will be included in the listing.

7.2.3 St Georges Respiratory Questionnaire (SGRQ)

The total SGRQ score and component scores (symptoms, activity and impact scores) will be calculated according to the SGRQ scoring manual. Total score as well as the component scores will be summarized by treatment and visit. Corresponding mean and CI plots over time will be provided as well as a listing by subject and visit. The listing will contain both response to the individual questions in SGRQ as well as the total and component scores.

7.2.4 Whole Lung Lavage

The number of subjects experiencing whole lung lavage (WLL), and the number of WLLs events will be summarized by visit and overall. The summary will also include event rates (95% CI) adjusted for time in trial since visit 1. A separate summary will present the number of subjects and the number of events between IMPALA and IMPALA-X. A WLL event is defined as a WLL procedure performed on a unilateral lung. These events are entered at visit 1 as part of the overall clinical assessment.

Time in trial is defined as the number of days from visit 1 to end of trial date.

Event rates shown as the number of events per subject year and the 95% confidence intervals (CI) of the event rates are estimated using a negative binomial model.

The 95% CI will be estimated using the below piece of code in SAS. Here the dataset wll_rate has the number of whole lung lavage by subject in parameter *aval*, and the logarithm of the time of exposure in parameter called *log_dur.* The parameter one has the value 1 (one) for all subjects. The dataset final include the estimated rate (esti), and the lower limit of the confidence interval (lowci) and the upper limit of the confidence interval (uppci).

```
ods output ParameterEstimates=ParameterEstimates;

proc genmod data= wll_rate;

class one;

model aval= one /cl noint dist=negbin offset=log_dur link=log  ;

lsmeans one / exp cl;

run;

data exp;

 set ParameterEstimates;

 where parameter="one";

 esti = exp(Estimate); * estimate;

 lowci = exp(LowerWaldCL); * lower limit of confidence interval;

 uppci = exp(UpperWaldCL); * upper limit confidence interval;

run;
```

Furthermore, the whole lung lavage will be summarized by location (left, right or both) and the volume of saline used will be summarized.

A listing of subjects requiring WLL including reasons for WLL, date of criteria met, and date of procedure will be provided.

7.2.5 Lung Function Test

The percentage predicted values (DLCO (%), FEV1 (%) and FVC (%)) will be summarized by visit.

DLCO % predicted will be haemoglobin (Hb) corrected according to the formula:

$$DLCO\ (\%\ predicted, Hb\ corrected) = 100\ \times \frac{DLCO\ (measured)}{DLCO(absolute\ predicted) \times 1.7Hb/(a + Hb)}$$

Where a is 10.22 for males and 9.38 for females, Hb must be measured in g/dL. Corresponding mean and CI plots over time will be provided.

All data will be listed including both actual and % predicted values of DLCO, FEV1 and FVC.

7.2.6 Disease Severity Score (DSS)

DSS will be summarized using N (%) in each category over time. Furthermore, a table showing number of subjects (N (%)) having improved/unchanged/worsened DSS score from visit 1 will be provided.

Assessment of DSS from subjects-visits where supplementary oxygen was used during arterial blood gas samples will be excluded from both summary tables.

A corresponding listing by subject and visit will be provided.

7.2.7 Need for Oxygen Supplement During the Trial

This endpoint will be assessed through the recordings of concomitant medication. The two medication classes V03AN and R07A will be selected.

Number of subjects requiring oxygen supplement any time during trial will be summarized by treatment and listed.

The summary will be repeated for oxygen supplement

- ongoing at baseline
- ongoing at end of trial
- ongoing at both baseline and end of trial
- started after baseline and stopped before end of trial

The listing will include further details as flow rate and regimen (dose, unit, route and frequency) as well as timing compared to baseline and end of trial (ongoing or stopped etc).

7.2.8 Overall Clinical Assessment

Overall clinical assessment consists of two endpoints as described below. Both endpoints will be summarized by treatment and visit.

- Status of aPAP (in remission, improving, stable or progressive)
- Requirement for treatment since last visit (no treatment required, treatment with inhaled molgramostim required, Whole Lung Lavage, oxygen supplementation or other treatment required)

7.3 Exploratory Endpoint

The exploratory endpoint is

- GM-CSF levels before and 2 hours after dosing

All values of GM-CSF above lower level of quantification (LLOQ) will be listed.

7.4 Handling of Missing Values

No imputation of missing data is planned.

7.5 Multiplicity Adjustments

No multiplicity adjustments are needed since no analyses are to be performed.

7.6 Subgroup and Site Effects

No subgroup analyses are planned.

Adjustments for site effects are not applicable since no analyses are performed.

8 Statistical Methodology for Safety Endpoints

Safety will be considered for subjects included in the Safety Analysis Set. *No imputation of missing data is planned for safety endpoints.*

8.1 Safety Parameters

The safety parameters are

- Adverse events
- Physical examination
- Vital signs
- ECG
- Laboratory safety assessments
- CT scan

8.1.1 Analysis and Presentation of Safety Parameters

8.1.2 Adverse Events

All adverse events (AEs) occurring after informed consent will be reported in the eCRF. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

Adverse events are considered treatment emergent if the onset of the events is on or after the first exposure date of IMP in this trial and until (estimated) last drug date + 7 days. Last drug date is defined as last kit date + 21 days or end of trial date whatever comes first. Only treatment emergent events will be included in the safety summaries.

Possible or probable related AE's are defined as ADRs.

Adverse events will be presented as described in section 7.1.

8.1.3 Physical Examination

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

Complete physical examinations will include at a minimum a review of the subject's general appearance, head, eyes, ears, nose, and throat (HEENT), neck, heart, lungs, abdomen, extremities, skin, and general neurological system.

No output will be generated for physical examination.

8.1.4 Vital Signs

Vital signs (heart rate, temperature, systolic and diastolic blood pressure) will be measured at each visit including an evaluation for each parameter.

Continuous values of vital signs will be summarized by parameter and visit including change from baseline.

8.1.5 Electrocardiogram (ECG)

A 12-lead ECG will be assessed using a standard ECG machine according to local procedures at the time points shown in Table 1.

Heart rate, QRS, PR and QT intervals will be recorded from the ECGs. The ECGs will be interpreted and signed and dated by the investigator or his/her designee.

The QT interval by be corrected using Fridericia's formula (QTcF) will be added to the summary tables as described below.

Continuous values of ECG will be summarized by parameter and visit including change from baseline.

8.1.6 Laboratory Safety Data

Laboratory safety parameters are listed described in Table 2. All results will be recorded in the eCRF and will be assessed as clinically significant or not clinically significant. Since local laboratories are used laboratory parameters will be converted to units as indicated in Table 2 before summarizing.

Table 2 Laboratory safety parameters

Category	Laboratory Parameter (unit)
Haematology	Haemoglobin (g/dL), RBC (10^12/L) Red Blood Cell Distribution Width (RDW) (%) Haematocrit (%) Mean cell volume (MCV) (fL) Mean cell haemoglobin (MCH) (pg) Mean cell haemoglobin concentration (MCHC) (g/dL) Platelet count (10^9/L) WBC and differential counts (absolute and percentage): Neutrophils (% and 10^9/L) Lymphocytes (% and 10^9/L) Monocytes (% and 10^9/L) Eosinophils (% and 10^9/L) Basophils (% and 10^9/L) Prothrombin Time International Normalised Ratio (PT-INR)
Clinical chemistry	Aspartate Aminotransferase (AST) (U/L) Alanine Aminotransferase (ALT) (U/L) Gamma Glutamyl Transpeptidase (GGT) (U/L) Alkaline Phosphatase (U/L) Bilirubin (mg/dL) Urea (mg/dL) S-Creatinine (mg/dL) Potassium (mmol/L) Sodium (mmol/L) Calcium (mg/dL) Chloride (mmol/L) Phosphate (mg/dL) Total protein (g/dL) Albumin (g/dL) C-Reactive Protein (CRP) (mg/dL) Glucose (non-fasting) (mg/dL)

Laboratory safety data will be summarized using descriptive statistics, including means, medians, SDs, and minimum and maximum by time point and treatment, including changes from baseline. In addition, laboratory safety data will be plotted using boxplots by time point and treatment.

A mean and CI plot over time will be presented for haemoglobin as well as for change from baseline in haemoglobin.

Abnormal values will be listed by subject, visit and safety parameter.

8.1.7 CT Scans

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

Results of the CT scans will be listed by subject and visit.

8.2 Safety Update

A safety update will be performed with a planned data cutoff 1-February 2019.

The output generated for the safety update is listed below. For the output in section 14.2.4 (Whole lung lavage) the date of the cutoff will be used to calculate subject years.

- Table 14.1.1, 14.1.3, 14.1.5, 14.1.6
- Tables 14.2.4.1, 14.2.4.3
- Table 14.2.6.1
- All output in section 14.3
- Listing 16.2.6.4

9 Deviations from Protocol

A safety analysis set has been added. At the time of protocol generation all patients were expected to be treated from the beginning of this trial. Since some patients are not treated in this trial it was decided to include a safety analysis set

The secondary endpoint “time off treatment after discontinuation of inhaled molgramostim” is not reported due to insufficient data collection.

10 Software

All statistical calculations described in this SAP will be done by BioStata Aps using SAS, release 9.4 or later (SAS Institute, Cary, NC, USA).

11 Reference List

St George's respiratory questionnaire manual version 2.3, 2019, Paul Jones

12 List of Listings

Listing 16.2.1.1 Violations of inclusion and/or exclusion criteria – screening failures

Listing 16.2.1.2 Individual subject disposition (all subjects)

Listing 16.2.1.3 Reason for withdrawal from trial (all subjects)

Listing 16.2.2.1 Protocol deviations (all subjects)

Listing 16.2.4.1 Individual subject demographics and baseline characteristics (all subjects)

Listing 16.2.4.2 Individual medical history (all subjects)

Listing 16.2.4.3 Individual concomitant medication (all subjects)

Listing 16.2.4.4 COVID-19 positive subjects (all subjects)

Listing 16.2.4.5 Adverse events occurring in COVID-19 positive subjects (all subjects)

Listing 16.2.4.6 Protocol deviations due to COVID-19 (all subjects)

Listing 16.2.5.1 Individual subject exposure (all subjects)

Listing 16.2.5.2 Individual subject relative exposure (all subjects)

Listing 16.2.5.3 Individual visits attended (all subjects)

Listing 16.2.6.1 Individual (A-a)DO_2 (all subjects)

Listing 16.2.6.2 Individual 6-minute walk test (all subjects)

Listing 16.2.6.3 Individual St Georges respiratory questionnaire scores (all subjects)

Listing 16.2.6.4 Individual whole lung lavage (all subjects)

Listing 16.2.6.5 Individual lung function tests (all subjects)

Listing 16.2.6.6 Individual disease severity scores (all subjects)

Listing 16.2.6.7 Subjects with oxygen supplement during trial (all subjects)

Listing 16.2.6.8 Individual overall clinical assessments (all subjects)

Listing 16.2.6.9 Individual GM-CSF measurements above lower level of quantification (all subjects)

Listing 16.2.7.1 Adverse events (all subjects)

Listing 16.2.7.2 Serious adverse events (all subjects)

13 List of Tables

Section 14.1

Table 14.1.10. Summary of missed key secondary endpoints assessments due to COVID-19 pandemic (safety analysis set)

Table 14.1.11 Summary of alternative endpoint ascertainment due to COVID-19 pandemic (safety analysis set)

Section 14.2

(14.2.1: Blood gas analysis endpoints)

Table 14.2.1.1 Summary of (A-a)DO_2 (mmHg) (full analysis set)

Table 14.2.1.2 Summary of change from baseline in (A-a)DO_2 (mmHg) (full analysis set)

(14.2.2: 6 minutes walking test endpoints)

Table 14.2.2.1 Summary of 6 minutes walking distance (m) (full analysis set)

Table 14.2.2.2 Summary of change from baseline in 6 minutes walking distance (m) (full analysis set)

Table 14.2.2.3 Summary of pre-walk dyspnoea score (Borg CR10) (full analysis set)

Table 14.2.2.4 Summary of change from baseline in 6 minutes walking distance (m) (full analysis set)

Table 14.2.2.5 Summary of post-walk dyspnoea score (Borg CR10) (full analysis set)

Table 14.2.2.6 Summary of change from baseline in dyspnoea score (Borg CR10) (full analysis set)

Table 14.2.2.7 Summary of SpO_2 at start of walk (%) (full analysis set)

Table 14.2.2.8 Summary of change from baseline in SpO_2 at start of walk (%) (full analysis set)

Table 14.2.2.9 Summary of worst SpO_2 during walk (%) (full analysis set)

Table 14.2.2.10 Summary of change from baseline in worst SpO_2 during walk (%) (full analysis set)

Table 14.2.2.11 Summary of desaturation during walk (%) (full analysis set)

Table 14.2.2.12 Summary of change from baseline in desaturation during walk (%) (full analysis set)

Table 14.2.2.13 Summary of completion of 6 minutes walking test (full analysis set)

(14.2.3: SGRQ endpoints)

Table 14.2.3.1 Summary of SGRQ total score (full analysis set)

Table 14.2.3.2 Summary of change from baseline in SGRQ total score (full analysis set)

Table 14.2.3.3 Summary of SGRQ symptoms score (full analysis set)

(14.2.4: Whole lung lavage endpoints)

(14.2.5: Lung function test endpoints)

(14.2.6: Disease severity score)

(14.2.7: Supplemental oxygen during trial)

Table 14.2.7.4: Summary of oxygen supplement ongoing at baseline and ongoing at end of trial (full analysis set)

Table 14.2.7.5: Summary of oxygen supplement started after baseline and stopped before end of trial (full analysis set)

(14.2.8: Overall clinical assessment)

Table 14.2.8.1 Summary of status of aPAP (full analysis set)

Table 14.2.8.2 Summary of requirement for treatment since last visit (full analysis set)

Section 14.3

(14.3.1: Adverse events)

Table 14.3.1.1 Overview of adverse events (safety analysis set)

Table 14.3.1.2 Summary of treatment emergent adverse events by SOC and preferred term (safety analysis set)

Table 14.3.1.3 Summary of treatment emergent adverse events by preferred term - frequency ≥ 5% (safety analysis set)

Table 14.3.1.4 Summary of treatment emergent adverse events by severity and SOC and preferred term (safety analysis set)

Table 14.3.1.5 Summary of treatment emergent adverse events by relationship and SOC and preferred term (safety analysis set)

Table 14.3.1.6 Summary of treatment emergent adverse events by outcome and SOC and preferred term (safety analysis set)

Table 14.3.1.7 Summary of treatment emergent serious adverse events by SOC and preferred term (safety analysis set)

Table 14.3.1.8 Summary of treatment emergent serious adverse events by severity, SOC and preferred term (safety analysis set)

Table 14.3.1.9 Summary of treatment emergent serious adverse events by relationship, SOC and preferred term (safety analysis set)

Table 14.3.1.10 Summary of treatment emergent serious adverse events by outcome, SOC and preferred term (safety analysis set)

Table 14.3.1.11 Summary of treatment emergent non-serious adverse events by SOC and preferred term (safety analysis set)

Table 14.3.1.12 Summary of treatment emergent non-serious adverse events by preferred term - frequency ≥ 5% (safety analysis set)

Table 14.3.1.13 Summary of treatment emergent non-serious adverse events by severity, SOC and preferred term (safety analysis set)

Table 14.3.1.14 Summary of treatment emergent non-serious adverse events by relationship, SOC and preferred term (safety analysis set)

Table 14.3.1.15 Summary of treatment emergent non-serious adverse events by outcome, SOC and preferred term (safety analysis set)

Table 14.3.1.16 Summary of treatment emergent adverse drug reactions by SOC and preferred term (safety analysis set)

Table 14.3.1.17 Summary of treatment emergent adverse drug reactions by severity, SOC and preferred term (safety analysis set)

Table 14.3.1.18 Summary of treatment emergent adverse drug reactions by relationship, SOC and preferred term (safety analysis set)

Table 14.3.1.19 Summary of treatment emergent adverse drug reactions by outcome, SOC and preferred term (safety analysis set)

Table 14.3.1.20 Summary of treatment emergent adverse events leading to treatment discontinuation by SOC and preferred term (safety analysis set)

Table 14.3.1.21 Summary of treatment emergent adverse events leading to treatment discontinuation by severity, SOC and preferred term (safety analysis set)

Table 14.3.1.22 Summary of treatment emergent adverse events leading to treatment discontinuation by relationship, SOC and preferred term (safety analysis set)

Table 14.3.1.23 Summary of treatment emergent adverse events leading to treatment discontinuation by outcome, SOC and preferred term (safety analysis set)

(14.3.2: Vital signs)

Table 14.3.2.1 Summary of vital signs (safety analysis set)

Table 14.3.2.2 Summary of change from baseline in vital signs (safety analysis set)

(14.3.3: ECG)

Table 14.3.3.1 Summary of electrocardiogram (ECG) (safety analysis set)

Table 14.3.3.2 Summary of change from baseline in electrocardiogram (ECG) (safety analysis set)

(14.3.4: Safety lab)

Table 14.3.4.1 Summary of hematology parameters (safety analysis set)

Table 14.3.4.2 Summary of change from baseline in hematology parameters (safety analysis set)

Table 14.3.4.3 Summary of clinical chemistry parameters (safety analysis set)

Table 14.3.4.4 Summary of change from baseline in clinical chemistry parameters (safety analysis set)

14 List of Figures

Section 14.2

(14.2.1: Blood gas analysis endpoints)

(14.2.2: 6 minutes walking test endpoints)

(14.2.3: SGRQ endpoints)

Section 14.3

(14.3.1: safety lab)