SAV008-01

An open-label, non-controlled, multicentre, pilot clinical trial of inhaled molgramostim in subjects with antibiotic-resistant non-tuberculosis mycobacterial (NTM) infection

NCT03421743

Statistical Analysis Plan

Version 1.0

19 February 2020

STATISTICAL ANALYSIS PLAN

An Open-label, Non-controlled, Multicentre, Pilot Clinical Trial of Inhaled Molgramostim in Subjects with Antibiotic-resistant Non-tuberculosis Mycobacterial (NTM) Infection

Protocol No.: *SAV008-01*

Product Code: *Molgramostim Nebulizer Solution (Molgradex®) 300 µg*

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use on the SAV008-01 study:

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1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data from the SAV008-01 study.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. In addition, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design

This is an open-label, non-controlled, multicentre, pilot clinical trial of inhaled molgramostim in subjects with persistent pulmonary NTM infection.

The study will comprise a Screening Visit, Baseline Visit, a 48-week treatment period and a 12-week follow up period. The Screening Visit (Visit 1) will be conducted up to 10 weeks prior to the Baseline Visit (Visit 2) to determine eligibility. Adult subjects with a history of chronic NTM infection with at least 2 positive cultures in the prior two years, of which at least one is within the last 6 months prior to Screening, will be considered for enrolment. Subjects should provide a positive NTM sputum culture at Screening to be eligible.

The study will include 30 subjects.

The treatment period will consist of 14 trial visits (Screening, Baseline, and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48; Visits 1-14) and a follow-up visit (Visit 15) 12 weeks after end of treatment. The visits at Weeks 28, 36 and 44 (Visits 9, 11 and 13) will include a telephone contact, all other visits will include a clinic visit.

At the Baseline Visit (Visit 2), eligible subjects will start treatment with inhaled molgramostim administered via the PARI eFlow nebulizer.

At each visit (Visits 1-15), sputum samples for staining and microscopy, and microbiological culture will be collected. If required, induced sputum may be obtained according to local standards. On the days of clinic visits (Visits 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15), subjects will be asked to collect two additional sputum samples at home, preferably on the consecutive days after the site visit (At the commencement of the study, only 1 sample was required for Visits 2 to 7, with the additional sampling added in protocol amendment(s)). On the days of the telephone contact visits (Visits 9, 11 and 13), three sputum samples will be collected at home, preferably on consecutive days.

Any AEs will also be collected at Baseline and all subsequent visits (Visits 2-15), At all clinic visits a pregnancy test/contraceptive check will be conducted, changes in concomitant medication, measurement of body weight and an assessment of DLCO will be performed. A computed tomography (CT) scan will be conducted at Baseline (Visit 2) if not performed within 6 months prior to Baseline. If DLCO drops by at least 20% at two consecutive visits the CT scan may be repeated. A CT scan can be performed after 48 weeks of treatment if this is a part of the local routine clinical practice.

A physical examination and an electrocardiogram (ECG) will be performed at Screening and Weeks 24 and 48 (Visits 1, 8 and 14) and vital signs will be collected at Screening, Baseline, and Weeks 4, 12 24, 32, 40 and 48 (Visits 1, 2, 3, 5, 8, 10, 12 and 14). Spirometry will be conducted at Baseline and at Weeks 12, 24, 32, 40 and 48 (Visits 2, 5, 8, 10, 12 and 14). A

6MWT will be conducted at Baseline, at Weeks 12, 24 and 48 and at the 12-week follow-up visit (Visits 2, 5, 8, 14 and 15). Blood samples for safety laboratory testing will be taken at Screening, Baseline, and at Weeks 4, 12, 24, 32, 40, 48 and at the 12-week follow-up visit (Visits 1, 2, 3, 5, 8, 10, 12, 14, 15). Anti-GM-CSF will be assessed at Baseline, at Week 4, 12, 24, 32, 48 and at the 12-week follow-up visit (Visits 2, 3, 5, 8, 10, 14 and 15). Subject reported outcomes (QoL-B, LRTI-VAS and GRH) will be assessed at Baseline and at all post Baseline clinic visits (Visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15). For subjects having a chest X-ray during the study period as part of the routine local clinical practice, the results from the X-ray will be recorded.

Participating subjects will be encouraged to contact the clinic between visits if they experience adverse events (AEs), worsening of their condition or have any other concerns. If needed, unscheduled visits will be conducted at investigator's discretion.

Treatment with inhaled molgramostim will be given at a dosage of 300 µg once daily for 48 weeks. All subjects in the trial initially consented to 24 weeks of treatment. All enrolled subjects continuing with 48 weeks of treatment will re-consent and follow the visits schedule as described above.

Subjects that do not wish to continue to 48 weeks of treatment will end treatment after 24 weeks (visit 8) and will attend the follow-up visit 12-weeks later as per the visit schedule outlined in Protocol Version 2.0 or 3.0.

Subjects who complete the initial 24-week treatment period prior to the approval of Protocol Version 4.0 will proceed to the 12-week follow up as per the visit schedule in Protocol Version 2.0 or 3.0. Once Protocol Version 4.0 is approved they will be asked to re consent and re-initiate treatment. This will occur at the next trial visit or at an unscheduled visit. These subjects will not receive the whole 48-week treatment. The will receive treatment for an additional 24 weeks minus the number of weeks that they have been in follow up.

Subjects that do not wish to re consent and re initiate treatment will stay in follow up and attend the follow-up visit as per the visit schedule outlined in Protocol Version 2.0 or 3.0.

At Baseline and at Weeks 4, 12, 24, 32 and 40 (Visits 2, 3, 5, 8, 10 and 12), dosing will take place in the clinic after blood sampling. A data review was conducted after the first 6 subjects had completed 12 weeks of treatment. If safety concerns or poor tolerability were identified in this review, the review committee might decide on less frequent dosing for subsequent subjects in the study. The review was conducted on 16 September 2018 and concluded that there were no safety issues of significant concern and the dose was unchanged. In order to obtain more robust treatment responses it was decided to extend the treatment duration from 24 to 48 weeks. Any changes to the conduct of the study such as change of dose, dose regimen or duration will be documented in a protocol amendment.

During the study, subjects in Group 1 will continue use of antimycobacterial treatment. All changes in antimycobacterial treatment will be recorded, including reasons for each change. In case of worsening of NTM pulmonary disease, antimycobacterial treatment may be added or a dosage increase of antimycobacterial treatment may be applied as rescue treatment, according to investigator's discretion.

2.2 Objectives

2.2.1 *Primary objective*

The primary objective is:

- To investigate efficacy of inhaled molgramostim on NTM sputum culture conversion to negative.

2.2.2 *Secondary objective(s)*

The secondary objectives are:

- To investigate efficacy of inhaled molgramostim on NTM sputum smear conversion to negative.
- To investigate efficacy of inhaled molgramostim on reduction of NTM bacterial load in sputum.
- To investigate efficacy of inhaled molgramostim on exercise capacity.
- To investigate efficacy of inhaled molgramostim on Subject Reported Outcomes.
- To investigate safety of inhaled molgramostim in subjects with NTM infection.

2.3 Sample Size

It was planned that 30 subjects will be enrolled. No formal sample size calculation was done as this is an initial pilot study.

2.4 Treatment Assignment and Randomisation

At the Baseline visit, all subjects found to be eligible according to the inclusion/exclusion criteria will be classified into the following treatment groups:

- Group 1: Subjects who remain sputum culture positive while currently on a multidrug NTM guideline based antimycobacterial regimen, which has been ongoing for at least 6 months prior to the Baseline Visit.
- Group 2: Subjects who remain sputum culture positive but have either stopped a multidrug NTM guideline based antimycobacterial regimen at least 28 days prior to Screening due to lack of response or intolerance, or never started such treatment.

Subjects successfully assigned to a subgroup will then start treatment with open-label molgramostim nebulizer solution.

3. STATISTICAL CONSIDERATIONS

3.1 Analytical Approach

Data analysis will be performed according to Southern Star Research's Standard Operating Procedures (SOPs).

The general analytical approach for all endpoints will be descriptive in nature. All summaries will present the data by treatment group as well as by all subjects combined.

Unless otherwise stated, the following statistical approaches will be taken:

Continuous variables:	Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the eCRF; mean, median, and SD will be presented to one more decimal place than the raw data.
Categorical variables:	Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population with non-missing data.
Multiplicity:	As this is an exploratory study no adjustments for multiplicity will be applied.
Confidence intervals (CIs):	CIs will be two-sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level.
Unscheduled Visits	Unscheduled visits will be excluded from summary tables.

3.2 Data Capture

3.2.1 *Database*

The primary method of data collection is via the study database, developed within the chosen Electronic Data Capture (EDC) platform, IBM Clinical Development. The database has been designed based on the final protocol, the system/core configuration, electronic Case Report Form (eCRF) specifications and/or mock eCRF and consistency check specifications.

Data will be entered directly into the EDC system.

Site-collected data will be entered directly from source notes at the site and will be verified by Clinical Research Associates (CRAs) to ensure data integrity.

This study also includes subject reported outcomes collected through ePRO entry within the EDC.

Refer to the Data Management Plan for further details.

3.2.2 *Third Party Data*

3.2.2.1 *Safety Laboratory*

Central safety laboratory data will be received from BARC Global Central Laboratory as specified in the BARC Data Transfer Specification. Data transfers are being processed on a monthly basis throughout the study, with each transfer being reconciled against the CRF data.

The final data transfer will be incorporated into the End of Study analysis once the final transfer has been received, reconciled and any issues are considered resolved.

No conversion of laboratory data will be performed.

3.2.2.2 *Anti-GM-CSF*

Anti-GM-CSF data will be received from Bioagilytix Europe GMBH as specified in the Bioagilytix Data Transfer Specification. Two data transfers will take place. The first transfer will occur following analysis of samples up to Visit 5 for the first six subjects and the second transfer will occur at End of Study.

The End of Study data transfer will be incorporated into the End of Study analysis once the transfer has been received, reconciled and any issues are considered resolved.

3.2.2.3 *Microbiology Analysis (Australia)*

Microbiology analysis of samples from Australian sites will be analysed and reported by Sullivan Nicolaides Pathology (SNP) as specified in the SNP Data Transfer Specification. Data transfers are being processed on a monthly basis throughout the study, with each transfer being reconciled against the CRF data.

The final data transfer will be incorporated into the End of Study analysis once the final transfer has been received, reconciled and any issues are considered resolved.

3.2.2.4 *Microbiology Analysis (UK)*

Microbiology analysis of samples from UK sites will be analysed and reported by Royal Brompton Hospital (RBH) as specified in the RBH Data Transfer Specification. Data transfers are being processed on a monthly basis throughout the study, with each transfer being reconciled against the CRF data.

The final data transfer will be incorporated into the End of Study analysis once the final transfer has been received, reconciled and any issues are considered resolved.

3.3 Statistical Programming

3.3.1 *CDISC*

3.3.1.1 *SDTM*

All study datasets will be structured according to Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) conventions as detailed in Table 1.

Table 1: SDTM Specifications and Deliverables

Deliverable	Specification
SDTM convention	SDTM Model v1.4, SDTMIG v3.2
CDISC Validator	Pinnacle21 v2.2.0 or later
SAS Version	V 9.4, vlatin1
SDTM Export Datasets	*.xpt
SDTM Annotated CRF	Required, aCRF.pdf in searchable pdf with required colour annotation
Define.XML	Required, v2.0.0
Study Data Reviewer's Guide	Required, sdrg.pdf

3.3.1.2 *ADaM*

Analysis datasets will be structured according CDISC Analysis Data Model (ADaM) conventions as detailed in Table 2.

Table 2: ADaM Specifications and Deliverables

Deliverable	Specification
ADaM convention	ADaMIG v1.1
CDISC Validator	Pinnacle21 v2.2.0 or later
SAS Version	V 9.4, vlatin1
ADaM Export Datasets	*.xpt
Define.XML	Required, v2.0.0
Analysis Data Reviewer's Guide	Required, adrg.pdf (paper size - Letter)

3.3.2 *Study Terminology*

Study-specific standard terms are detailed in Table 3.

Table 3: Study CDISC Terminology

Subject Elements	Screen (SCRN) Molgramostim (MOLG) Follow-Up (FU)
Epochs	SCREENING OPEN LABEL TREATMENT FOLLOW-UP
Treatment Arms	GROUP 1 GROUP 2
Visit Numbers / Visits	SCREENING EPOCH 1.0 Screening TREATMENT EPOCH 2.0 Baseline Visit* 3.0 Week 4 4.0 Week 8 5.0 Week 12 6.0 Week 16 7.0 Week 20 8.0 Week 24 9.0 Week 28 10.0 Week 32 11.0 Week 36 12.0 Week 40 13.0 Week 44 14.0 Week 48 888 Early Discontinuation 999 End of Study FOLLOW-UP EPOCH 15.0 Follow Up Visit Unscheduled visits: x.n where x is the visit number of the closest previous scheduled visit and n is the sequence number of the unscheduled visit, restarting at 1 after each scheduled visit. EPOCH will be assigned according to the epoch of the closest previous visit. * “Baseline Visit” will be used when referring to Visit 2. The term “Baseline” will also be used as detailed in 3.3.3.

3.3.3 *Baseline*

For sputum data, baseline will be derived from the combined pre-treatment visits (i.e. Screening and Baseline), where at least one positive sample will be assigned as positive as baseline. For gradings, the most severe/highest grade will be used.

For all other parameters, baseline will be defined as the last available assessment prior to first study drug administration.

3.3.4 *Change from Baseline*

Absolute change from Baseline will be calculated as:

$$Absolute\ change\ from\ baseline = (postbaseline\ value) - baseline\ value$$

3.3.5 *Listings, Tables and Figures*

Listings, tables and figures will be delivered as individual .rtf files in accordance with the mock listings, tables and figures.

Data listings will present all data, with subjects grouped by Group.

Tabulations will summarise data by Group and Total.

4. ANALYSIS SETS

One (1) analysis dataset will be used for study all analyses: Full Analysis Set (FAS).

Additional analysis sets or subgroups of interest may be required as part of post-hoc analyses. These will be detailed in the CSR.

The number and percentage of subjects in each analysis set will be summarised.

4.1 Analysis Set Descriptions

4.1.1 *Full Analysis Set (FAS)*

The FAS will comprise all subjects enrolled into the study.

5. PROTOCOL DEVIATIONS

Analysis Set: Full Analysis Set (FAS)

All deviations recorded during the trial will be categorised as Minor and Major. The major deviations will be further assessed in order to identify critical deviations. A critical protocol deviation will be defined as a deviation that contributes to the following:

- Treatment compliance below 80 % during the treatment period.
- No sputum samples at 2 visits.

6. SUBJECT DISPOSITION

Analysis Set: Full Analysis Set (FAS)

A listing of subject disposition will present:

- Date of informed consent
- Date of treatment commencement
- Date of treatment discontinuation
- Study day of treatment discontinuation (Days after first dose)
- Last visit before treatment discontinuation
- Primary reason for discontinuation of treatment
- Date of study completion/End of participation
- Study day of study completion/End of participation (Days after first dose)
- Last visit before study completion/End of participation
- Primary reason for ending study participation

Subject withdrawal information, including date and reason for treatment termination, will also be listed in a separate listing.

The number and percentage of subjects entering and discontinuing the study will be summarised along with the reason for discontinuation. The subject disposition summary table will include:

- Number of subjects enrolled
- Number of subjects who received at least one dose of study medication
- Number of subjects who completed 24 weeks treatment
- Number of subjects who completed 48 weeks treatment
- Number of subjects who completed the full study
- Number of subjects withdrawn early
- Reason for early withdrawal

7. DEMOGRAPHIC AND BASELINE INFORMATION

Analysis Set: Full Analysis Set (FAS)

7.1 Demographics

7.1.1 *Definition of variables*

- Age (years)
- Sex
- Race (White/Asian/Black/American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander)
- Female reproductive status
- Male reproductive status
- Smoking status (Previous/Current/Never)

7.1.2 *Biostatistical methods*

Demographic data will be listed and summarised.

7.2 Baseline Characteristics

Select baseline characteristics will be presented in a summary table, including:

- Height
- Weight
- BMI
- FVC
- FEV1

7.3 Medical history

All medical history data will be listed. Medical history (other than disease under study) will be coded using the Medical Dictionary for Regulatory Activities, MedDRA® and summarised by system organ class (SOC) and preferred term (PT).

7.4 Pregnancy Test

Pregnancy test data will be listed for all women of childbearing potential.

7.5 Eligibility

All eligibility data will be listed.

7.6 Disease specific Medical History

7.6.1 *Definition of variables*

From the CRFs:

- Date of microbiological diagnosis of current pulmonary infection
- Type of NTM (Mycobacterium avium complex (MAC) | Mycobacterium abscessus)
- Body weight at time of initial diagnosis
- Age at time of initial diagnosis
- Forced Vital Capacity (FVC) at time of initial diagnosis
- Forced Expiratory Volume in 1 second (FEV1) at time of initial diagnosis
- ATS/IDSA 2017 criteria fulfilled

Derived:

- Duration of infection: defined as the number of days from the date of initial diagnosis to the date of informed consent.

7.6.2 *Biostatistical methods*

NTM history data will be listed for all subjects.

An NTM History summary table will present:

- Duration of infection
- Frequency of NTM type
- Forced Vital Capacity (FVC) at time of initial diagnosis
  - FVC (L)
  - Relative FVC (%)
- Forced Expiratory Volume in 1 Second (FEV1) at time of initial diagnosis:
  - FEV1 (L)
  - Relative FEV1 (%)
- Number of subjects with each ATS/IDSA2017 criterion

7.7 NTM Sampling

All NTM sampling history will be listed.

8. TREATMENT EXPOSURE

Analysis Set: Full Analysis Set (FAS)

8.1.1 *Definition of variables*

From the CRFs:

- Confirmation of subject training
- Date/time of clinic study drug administration
- Dispense data
  - Number of kits dispensed by visit
- Compliance data
  - Number of used vials
  - Number of unused vials
  - Number of used lost vials
  - Number of unused lost vials
  - Compliance (visit level)
- Dose change details
  - Start date of changed dose regimen
  - Number of doses
  - Frequency of dose
  - Reason for changed dose

Derived:

- Number of subjects who had a break in treatment after completing Week 24 and commencing the remaining treatment period to Week 48

- Duration of exposure:

$$date\ of\ treatment\ discontinuation\ -\ date\ of\ first\ treatment\ +\ 1$$

- Overall compliance (%)

$$\frac{Number\ of\ used\ vials}{Treatment\ days\ *} x100$$

* $treatment\ days\ = (date\ of\ end\ of\ treatment\ -\ date\ of\ visit\ 2) + 1$

8.1.2 *Biostatistical methods*

All treatment exposure data, including kit dispense, compliance, study drug administration and dose change details, will be listed.

Duration of exposure and compliance (by visit and overall) will be summarised.

9. EFFICACY

Analysis Set: Full Analysis Set (FAS)

9.1 Endpoints

9.1.1 *Primary Efficacy Endpoint:*

- Sputum culture conversion defined as at least three consecutive negative sputum samples during the treatment period.

9.1.2 *Secondary Efficacy Endpoints:*

- Sputum smear conversion defined as at least three consecutive negative AFB stained sputum smears on microscopy during the treatment period in subjects who were smear positive at Baseline.
- Durability of sputum culture conversion (defined as conversion at or before Week 48 and culture still negative at 12-weeks follow-up).
- Durability of sputum smear conversion (defined as conversion at or before Week 48 and smear still negative at 12-weeks follow-up).
- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.
- Change in semi-quantitative grade of sputum cultures from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.
- Change in symptom scores (assessed using Lower Respiratory Tract Infections – Visual Analogue Scale (LRTI-VAS) and Quality of Life Questionnaire– Bronchiectasis (QOLB) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in Global Rating of Health (GRH) from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in body weight from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and 12-week follow-up.
- Change in 6MWD, oxygen desaturation and Borg CR10 scores during a 6MWT from Baseline to Week 12, 24, 48 and 12-week follow-up.

9.2 Variables

9.2.1 *Primary Endpoint Variables*

- Sputum culture conversion during the treatment period defined as all available samples from three consecutive visits to be negative
- The time of culture conversion: Defined as the time the first of three consecutive visits with 100% negative samples was obtained. Subjects with no conversion will be censored at the date of their last visit.

9.2.2 *Secondary Endpoint Variables*

- Sputum smear conversion: Defined as at least three consecutive visits with 100% negative AFB stained sputum smears on microscopy during the treatment period in subjects that were smear positive at Baseline.
- Durability of sputum culture conversion: Defined as conversion at or before Week 48 and culture still negative at 12-weeks follow-up (with no positives in between).
- Durability of sputum smear conversion: Defined as conversion at or before Week 48 and smear still negative at 12-weeks follow-up (with no positives in between).
- Change from baseline in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears
- Change from baseline in semi-quantitative grade of sputum cultures (measured by time to positivity and exploratory quantitation of cultures)
- Change from baseline in symptom scores
    - Lower Respiratory Tract Infections – Visual Analogue Score (LRTI-VAS)
    - Quality of Life Questionnaire – Bronchiectasis (QOL-B)
- Change from baseline in Global Rating of Health (GRH)
- Change from baseline in body weight
- Change from baseline in 6MWD, oxygen desaturation and Borg CR10 scores

9.3 Biostatistical methods

9.3.1 *Primary Endpoint*

9.3.1.1 *Sputum Culture Conversion*

Sputum culture conversion data will be listed, including time of culture conversion.

Sputum culture conversion rates (number of subjects who convert to negative out of the number per group) will be presented with 95% exact binomial confidence intervals.

On the basis of the poor historical success rates of current standard therapy, a 30% response rate for the primary endpoint will be considered clinically relevant.

Time to culture conversion will be evaluated using Kaplan Meier estimates, with 95% confidence intervals.

9.3.1.2 *Sensitivity Analyses*

In a sensitivity analysis, culture conversion will be re-defined as requiring at least 2 samples are available from each of the three consecutive visits. Sputum culture conversion rates and time to culture conversion will be analysed as part of this sensitivity analysis.

9.3.2 *Secondary Endpoints*

9.3.2.1 *Sputum Smear Conversion (Primary)*

Sputum smear conversion will be evaluated and presented in the same way as the primary endpoint for culture conversion.

9.3.2.2 *Sputum Smear Conversion (Sensitivity)*

In a sensitivity analysis, smear conversion will be re-defined as requiring at least 2 samples are available from each of the three consecutive visits. Sputum smear conversion rates and time to smear conversion will be analysed as part of this sensitivity analysis.

9.3.2.3 *Mycobacterial Microscopy Grading*

Mycobacterial microscopy data will be listed for each sample, including AFB positivity and AFB semi-quantitative grading. The listing will also include the overall visit AFB positivity and grading statuses. Laboratory grading terminology will be re-named as detailed in Table 4.

Table 4: Mycobacterial Microscopy Grading

SNP	RBH	Cross-Tabulation
No acid fast bacilli seen	No AFB Seen	Negative
Acid fast bacilli – occasional	Scanty AFB Seen +/-	Scant
Acid fast bacilli +	Moderate AFB Seen 1+	1+
Acid fast bacilli ++	Moderate AFB Seen 2+	2+
Acid fast bacilli +++	AFB Seen 3+	3+
Acid fast bacilli ++++		4+

The number of subjects who decrease over the scale (and proportion out of the number per group) will be presented with 95% exact binomial confidence intervals.

A summary table will present continuous descriptive statistics of grade for each scheduled visit.

9.3.2.4 *Mycobacterial Culture Grading*

Mycobacterial culture data will be listed for each sample, including culture positivity, culture semi-quantitative grading, time to detection in liquid media (MGIT) and organisms isolated. The listing will also include the overall visit AFB positivity and grading statuses.

The following is noted:

- MGIT and semi-quantitative grading will need to be extracted from the Comment column in the SNP data transfer.
- Semi-quantitative grading is not available for mycobacterial culture data from RBH.

For each scheduled visit, the number of subjects (and proportion out of the number per group) who report a decreased culture grade compared to Baseline will be presented with 95% exact binomial confidence intervals. Where multiple samples were taken at a visit, the worst grade will be used for comparison to Baseline.

A figure will present the mean change from baseline of semi-quantitative sputum culture grades, with error bars representing the standard deviation.

9.3.2.5 *Symptom Scores*

Symptoms scores (assessed using LRTI-VAS and QOL-B) will be listed for all subjects.

Scoring of LRTI-VAS
Separate scores will be calculated for each symptom and a total score will be calculated, consisting of all symptom scores added up, where the same weight is assigned to all symptom domains.

Symptom and total scores will not be calculated for LRTI-VAS records with missing data.

A summary table will present a summary of total scores, including actual values and change from Baseline, by group and overall, for all scheduled visits.

Scoring QOL-B
QOL-B data will be scored according to the Manual Scoring Instructions for QOL-B Version 3.1 and domain scores will be presented in a separate listing.

A summary table will present a summary of domain scores, including actual values and change from Baseline, by group and overall, for all scheduled visits.

9.3.2.6 *Global Rating of Health (GRH)*

Global Rating of Health (GRH) data will be listed for all subjects.

A summary table will present a summary of actual values and change from Baseline, by group and overall, for all scheduled visits.

9.3.2.7 *Body Weight*

Body weight will be listed for all subjects.

A summary table will present a summary of actual values and change from Baseline, by group and overall, for all scheduled visits.

9.3.2.8 *6 Minute Walk Test*

6 Minute Walk Test data, including distance walked (6MWD), oxygen saturation (SpO_2) before and during the test as well as oxygen desaturation (delta SpO_2) and Borg (CR-10) Dyspnoea scores before and after the test, will be listed for all subjects.

A summary table will present a summary of actual values and change from Baseline, by group and overall, for all scheduled visits, for the following variables:

- Dyspnoea Score (Borg CR-10) (pre and post walk)
- Blood oxygen saturation (SpO2) pre walk
- Worst SpO2 during the walk
- Distance walked

The proportion of subjects that complete all 6 minutes walking during the test will be summarised for all scheduled visits.

Where the two scheduled 6MWT tests were performed at a given scheduled timepoint, the summary table will use the data from the assessment where the subject walked the longest distance.

10. SAFETY

Analysis Set: Full Analysis Set (FAS)

10.1 Safety Endpoints

- Number of AEs, SAEs, ADRs, severe AEs and AEs leading to treatment discontinuation during the trial period.
- Change in WBC and differentials in blood from Baseline to Weeks 4, 12 24, 32, 40, 48 and 12-week follow-up.
- Change in DLCO from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and at 12-week follow-up.
- Change in forced expiratory volume in 1 second (FEV1) (% predicted) and forced vital capacity (FVC) (% predicted) from Baseline to Weeks 12, 24, 32, 40 and 48.
- Development of anti GM-CSF antibodies at Week 4, 12, 24, 32, 48 and at 12-week follow-up.

10.2 Adverse Events

10.2.1 *Definition of variables*

- AE, any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
- Treatment Emergent Adverse Event (TEAE), defined as an AE that commences on, or after, the date of the first administration of study drug until and including the day of the 12-week Follow-up visit.
- Serious Adverse Event (SAE), as defined in the protocol section 12.16:
    - Results in death
    - Is life-threatening
    - Requires hospitalization or prolongation of existing hospitalization
    - Results in persistent or significant disability or incapacity
    - Is a congenital anomaly or birth defect
    - May jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above (Important Medical Events)
- Severity
    - Mild
    - Moderate
    - Severe
- Outcome
    - Not Recovered
    - Recovered
    - Recovered with Sequelae
    - Fatal
    - Unknown
- Causality, categorised as described in the protocol section 12.16:
    - Not applicable
    - Unlikely
    - Possible
    - Probable
- Causality (Binary categorisation), where:
    - Not related = Not Related or Unlikely
    - Related = Possible or Probable

- Actions taken with study drug
  - Dose delayed
  - Dose stopped
  - Treatment withdrawn
- Other actions taken
  - Medical procedure
  - Medication administered
  - Other

10.2.2 *Biostatistical methods*

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

All adverse events recorded during the study will be listed. All serious AE and AEs leading to treatment discontinuation and study withdrawal will be listed.

Summary tables will be produced for treatment emergent adverse events (TEAEs). The number and percentage of subjects with adverse events by system organ class (SOC) and preferred term (PT) will be tabulated. Similar summaries will be produced by severity and relatedness.

10.3 Deaths

All details relating to subject deaths will be presented in a Death listing.

10.4 Prior and Concomitant Medication

Concomitant therapies will be coded using the World Health Organization-Drug Reference List (WHODRL).

Prior and concomitant medications will be presented in separate listings. Medications stopped on the same day as first study drug administration will be considered as prior medication only. Both prior and concomitant listings will flag antimycobacterial treatments and include data related to changes of the patient's NTM treatment regimen and the reason for a change to patient's NTM treatment regimen.

Prior and concomitant medication summaries will be presented in separate tabulations, with data summarised by Anatomical Therapeutic Chemical (ATC) (Level 2) and Preferred Name (PN) using frequency counts and percentages. For the summaries of prior and concomitant medications, subjects who take the same medication (in terms of the PN) more than once will be counted only once for that medication. An additional concomitant medication table will be prepared to present antimycobacterial treatments.

10.5 Laboratory

10.5.1 *Definition of variables*

10.5.1.1 *Hematology*

- Basophils (absolute and %)
- Eosinophils (absolute and %)
- Hematocrit
- Hemoglobin
- Lymphocytes (absolute and %)
- MCH
- MCHC
- MCV
- Monocytes (absolute and %)
- Neutrophils (absolute and %)
- Platelet count
- Red blood cell count (RBC)
- Red Cell Distribution Width (RDW)
- White blood cell count (WBC)

10.5.1.1 *Chemistry*

- Alanine Aminotransferase (ALT)
- Albumin
- Alkaline phosphatase
- Aspartate Aminotransferase (AST)
- Calcium
- Chloride
- C-Reactive Protein (CRP)
- Estimated glomerular filtration rate (eGFR)
- Gamma Glutamyl Transpeptidase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphate
- Potassium
- S-Creatinine
- Sodium
- Total bilirubin
- Total protein
- Urea

10.5.1.1 *Urinalysis with Microscopy*

- Glucose
- Microalbuminuria
- pH
- Protein
- Red Blood Cells (RBC)
- White Blood Cells (WBC)

10.5.1.2 *Coagulation*

- PT-INR

10.5.2 *Biostatistical methods*

All laboratory parameters will be listed with flags for values outside the reference ranges and values considered to be clinically significant.

Each parameter will be summarised descriptively (including actual values and changes from baseline) for each scheduled visit. Shift tables will also be presented for hematology and chemistry variables.

10.6 Vital Signs

10.6.1 *Definition of variables*

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart rate (beats per minute)
- Respiratory Rate (breaths per minute)
- Body temperature (°C)

10.6.2 *Biostatistical methods*

Vital sign parameters will be listed for all subjects and time points, including assessment (normal, abnormal) and clinical significance (clinically significant, not clinically significant).

Observed values, as well as changes from baseline, will be summarised descriptively for all vital sign parameters for each planned assessment.

10.7 Body Measurements

10.7.1 *Definition of variables*

- Weight (kg)
- Height (cm) (Baseline only)

10.7.2 *Biostatistical methods*

Height and weight will be listed for all subjects and time points.

Refer to Section 9.3.2.6 regarding presentation of post-Baseline weight data.

10.8 Physical Examination

10.8.1 *Definition of variables*

- General appearance
- HEENT (Head, Eyes, Ears, Nose, Throat)
- Neck
- Cardiovascular
- Respiratory
- Abdomen
- Extremities
- Dermatological
- Neurological
- Other

10.8.2 *Biostatistical methods*

Physical examination data will be listed for all subjects and time points.

10.9 12-lead ECG

10.9.1 *Definition of variables*

- Heart rate (beats/minute)
- QRS interval (msec)
- PR interval (msec)
- QT interval (msec)
- ECG status (Normal/Abnormal) (Clinical significance will be flagged where abnormal)

10.9.2 *Biostatistical methods*

ECG parameters will be listed for all subjects and time points.

Observed values and change from baseline will be summarised descriptively for all ECG parameters for all planned assessments.

10.10 Pulmonary Function Tests

10.10.1 *DLCO*

DLCO data, including predicted DLCO and absolute DLCO will be listed. Predicted DLCO and average absolute DLCO measurement will be descriptively summarised by visit, including change from baseline. Percent predicted DLCO will be calculated as:

$$\%\ Predicted\ DLCO\ = \frac{Average\ DLCO}{Predicted\ DLCO}\ x\ 100$$

10.10.2 *Spirometry*

Spirometry data, including Absolute Forced Expiratory Volume in 1 second (FEV_1) and Absolute Forced Vital Capacity (FVC), will be listed. FEV_1 and FVC will be descriptively summarised by visit, including change from baseline.

Percent predicted FVC and FEV1 will be calculated using the GLI-2012 SAS Macro. Baseline height will be used for all derivations.

10.11 Radiology

10.11.1 *CT Scan*

CT scan data will be listed.

10.11.2 *Chest X-Ray*

Chest x-ray data will be listed.

10.12 Pregnancy Test

Pregnancy test data will be listed.

11. IMMUNOGENICITY

Analysis Set: Full Analysis Set (FAS)

11.1 Definition of variables

- Anti-GM-CSF antibodies
- Neutralising antibodies

11.2 Biostatistical methods

All immunogenicity data will be listed.

The incidence of anti-GM-CSF antibodies and neutralising antibodies in each treatment group by visit will be summarised by frequency counts and percentages (in a cumulative manner). Individual titre profiles will also be plotted by group.

12. HANDLING OF MISSING DATA

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

13. CHANGES TO THE PLANNED ANALYSIS

The following changes to the biostatistical methods planned in the protocol are defined below:

- The 5x5 cross-tabulation summaries of the semi-quantitative grading described in Section 13.2 of the protocol (Secondary Endpoints) has been replaced with alternative summary tabulations, in order to present the data in a clearer and useful way.

13.1 Interim Analysis

An interim analysis was not initially planned, nor incorporated into the protocol. A planned interim analysis was subsequently added.

14. INTERIM AND FINAL ANALYSIS

An interim analysis is planned for this study, focusing primarily on the microbiology data up to Week 16.

The following endpoints will be assessed:

- Sputum culture negative samples during the treatment period up to week 16,
- Sputum smear conversion, defined as at least three consecutive negative AFB stained sputum smears on microscopy during the treatment period (up to Week 16) in subjects who were smear positive at Baseline,
- Change in semi-quantitative grade of number of NTM on microscopy of AFB stained sputum smears from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.
- Change in semi-quantitative grade of sputum cultures from Baseline to Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 12-week follow-up.

Safety data (Adverse Events and laboratory data) will also be reviewed.

15. SOFTWARE

The following software will be used to perform the statistical analyses: SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

16. REFERENCES

1) Clinical Trial Protocol SAV008-01, Version 4.0, 4th Oct 2018
2) GLI-2012 - SAS Macro; Quanjer et al., GLI Spiro Eur Respir J. 2012 Dec 40(6):1324-43; Macro Version 2 - April 7, 2013 (https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/sas-macro.aspx)
3) Manual Scoring Instructions for QOL-B Version 3.1

17. APPENDIX 1: QOL-B SCORING MANUAL

Manual Scoring Instructions for QOL-B Version 3.1

Step 1: Item-by-item responses

The values assigned to participants' responses for each question are listed below. Enter them on the Item-by-Item Worksheet.

- For questions 1 – 4: A lot of difficulty = 1, Moderate difficulty = 2, A little difficulty = 3, No difficulty = 4
- For questions 5 – 11: Always = 1, Often = 2, Sometimes = 3, Never = 4
- For questions 12 – 15: Use the assigned number designated for each specific response
- For questions 16 – 26: Completely true = 1, Mostly true = 2, A little true = 3, Not at all true = 4
- For question 27: Use the assigned number designated for each specific response
- For question 28: Always = 1, Often = 2, Sometimes = 3, Never = 4
- For questions 29 – 31: A lot = 1, A moderate amount = 2, A little = 3, Not at all = 4
- For question 32: Clear = 1, Clear to yellow = 2, Yellowish-green = 3, Brownish-dark = 4, Green with traces of blood = 4, Don't know = 6
- For questions 33 – 37: Always = 1, Often = 2, Sometimes = 3, Never = 4

Step 2: Scoring multiple responses or skipped questions

If two responses are marked and there is no opportunity to ask the respondent which one is correct, the **worst response** should be selected for data entry and scoring. This provides a conservative estimate of their response to this item. For example, item #29 asks: "Have you felt congestion in your chest?" The response choices range from "A lot" to "Not at all." If the respondent marks "a lot" and "a moderate amount" you should enter "a lot" for this question.

Please note that some items are reverse-keyed and therefore, the worst response is not necessarily the lower number.

If participants skip a question, do not assign a response value (i.e. leave it blank).

Step 3: Scaling item 32 and reverse coding

Item 32 (resp32) has 5 possible answers that are scored and all other items on the QOL-B questionnaire have only 4 possible answers. Possible scores for resp32 are 1, 2, 3, 4, 5 (scored as 4) and 6 (not scored), whereas for other questions the possible scores are 1, 2, 3, and 4. Resp32 and eight other items are also reverse coded; because of the wording for these particular items, reverse coding is necessary to make higher scores correspond to better health outcomes. Reverse coding is conducted for resp32, and for health5, vital8, treat12, treat14, health15, role20, health24, and role27. These items are marked with an asterisk on the Item-by-Item Worksheet and the reverse-coded values are shown in the box on the worksheet.

For item 32:

Original value = Reverse-coded value
1 = 4
2 = 3
3 = 2
4 = 1
6 = Not scored

For item 19:

"doesn't apply" = Not scored

For items 5, 8, 12, 14, 15, 20, 24, 27:

Original value = Reverse-coded value
1 = 4
2 = 3
3 = 2
4 = 1

Step 4: Preparing to calculate scaled scores and missing values

Transfer the values from the Item-by-Item Worksheet to the Scaled Score Worksheet. For reverse-coded items, use the reverse-coded values. Do not enter any values for missing responses; leave the line blank. If the responses are missing for more than half the items in a scale, the score for that scale should not be calculated. Missing values are not imputed. Note that missing responses within a scale will change the number of points corresponding to a change of one answer category for one item for that respondent.

Step 5: Calculate the scaled scores

Calculate scores for the eight QOL-B domains using the formulas on the Scaled Score Worksheet. Note that a total QOL-B score is not calculated.

Item-by-Item Worksheet

Numbers correspond to items on the QOL-B Version 3.1 questionnaire. Fill in the values using the scoring rules described in steps 1 – 3.

1. _____
2. _____
3. _____
4. _____
5.* _____=_____
6. _____
7. _____
8.* _____=_____
9. _____
10. _____
11. _____
12.*_____=_____
13. _____
14.*_____=_____
15.*_____=_____
16. _____
17. _____
18. _____
19. _____
20.*_____=_____
21. _____
22. _____
23. _____
24.*_____=_____
25. _____
26. _____
27.*_____=_____
28. _____
29. _____
30. _____
31. _____
32.*_____=_____
33. _____
34. _____
35. _____
36. _____
37. _____

***Reverse-Coded Values**

For items 5, 8, 12, 14, 15, 20, 24, 27:

Original Value = Reverse-Coded Value
1 = 4
2 = 3
3 = 2
4 = 1

For item 32:

Original Value = Reverse-Coded Value
1 = 4
2 = 3
3 = 2
4 = 1
6 = Not scored

Scaled Scores Worksheet – Page 1 of 3

Enter the values from the Item-by-Item Worksheet. Use the reverse-coded values, if applicable. Do not enter any values for missing responses; leave the line blank. Assess the number of missing values and calculate scores as described in Steps 4 and 5 (see page 2).

Physical Functioning Domain (5 items)

1. _____
2. _____
3. _____
4. _____
16. _____

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Role Functioning Domain (5 items)

17. _____
20. _____
25. _____
27. _____
28. _____

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Vitality Domain (3 items)

6. _____
8. _____
9. _____

If 2 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Scaled Scores Worksheet – Page 2 of 3

Emotional Functioning Domain (4 items)
7. _____
10. _____
11. _____
23. _____

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Social Functioning Domain (4 items)
18. _____
19. _____ (* "doesn't apply" = Not scored)
22. _____
26. _____

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Treatment Burden Domain (3 items)
12. _____
13. _____
14. _____

If 2 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Health Perceptions Domain (4 items)
5. _____
15. _____
21. _____
24. _____

If 3 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Scaled Score Worksheet – Page 3 of 3

Respiratory Symptoms Domain (9 items)
29. _____
30. _____
31. _____
32. _____
33. _____
34. _____
35. _____
36. _____
37. _____

If 5 or more responses are missing, do not score this domain.
Scaled score = [((_____)-1)/3] x 100 = _____
mean of responses

Note: No total score is calculated.

SAS Programming Code for Scoring QOL-B V3.1

Note: To enter data, refer to **Step 1: Item-by-item responses,** and for decision rules regarding multiple responses or skipped questions, refer to **Step 2: Scoring multiple responses or skipped questions** (see page 1).

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

Data QOLB; set QOLB;

/* Rescaling Respiratory 32 */
if resp32=6 then resp32=.;
else if resp32=1 then resp32= 4;
else if resp32=2 then resp32= 3;
else if resp32=3 then resp32= 2;
else if resp32=4 then resp32= 1;
else if resp32=5 then resp32= 1;

/* Rescaling “doesn’t apply” Social 19 */
if social19=5 then social19=.;

/* Recoding Some Variables */
health5=5-health5;
vital8=5-vital8;
treat12=5-treat12;
treat14=5-treat14;
health15=5-health15;
role20=5-role20;
health24=5-health24;
role27=5-role27;
run;

/* Calculating Scores */

Data QOLB; set QOLB;
if nmiss (phys1, phys2, phys3, phys4, phys16) <= 2 then
physical = (mean (phys1, phys2, phys3, phys4, phys16)-1)/3*100;

if nmiss (role17, role20, role25, role27, role28) <= 2 then
role = (mean (role17, role20, role25, role27, role28)-1)/3*100;

if nmiss (vital6, vital8, vital9) <= 1 then
vitality = (mean (vital6, vital8, vital9)-1)/3*100;

if nmiss (emot7, emot10, emot11, emot23) <= 2 then
emotion = (mean (emot7, emot10, emot11, emot23)-1)/3*100;

if nmiss (social18, social19, social22, social26) <= 2 then
social = (mean (social18, social19, social22, social26)-1)/3*100;

if nmiss (treat12, treat13, treat14) <= 1 then
treat = (mean (treat12, treat13, treat14)-1)/3*100;

if nmiss (health5, health15, health21, health24) <= 2 then
health = (mean (health5, health15, health21, health24)-1)/3*100;

if nmiss (resp29, resp30, resp31, resp32, resp33, resp34, resp35, resp36, resp37)
<= 4 then respirat = (mean (resp29, resp30, resp31, resp32, resp33, resp34,
resp35, resp36, resp37)-1)/3*100;
run;
```