Official Title: A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Validate Patient-Reported Outcome Instruments in Adult Subjects With Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by Mycobacterium avium Complex (MAC)

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STATISTICAL ANALYSIS PLAN

ARISE - A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Validate Patient-Reported Outcome Instruments in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by *Mycobacterium avium* Complex (MAC)

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CONFIDENTIALITY STATEMENT

Approval

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALIS	amikacin liposome inhalation suspension
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AZI	azithromycin
BDRM	Blinded data review
BMI	body mass index
CM	concomitant medication
COPD	chronic obstructive pulmonary disease
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EAR	exposure-adjusted incidence rate
eCDF	empirical cumulative distribution functions
eCRF	electronic case report form
ELC	empty liposome control
EOS	end of study
EOT	end of treatment
eCDF	empirical cumulative probability function
ETH	ethambutol
EXACT	EXAcerbations of Chronic Pulmonary Disease Tool
EXACT RS	EXAcerbations of Chronic Pulmonary Disease Tool - Respiratory Symptoms
FACIT	Functional Assessment of Chronic Illness Therapy
FEV_1	forced expiratory volume in 1 second
ICE	intercurrent events
ICF	Informed Consent Form
ITT	intent-to-treat
IWRS	Interactive Web Response System
LS-mean	least square mean

Abbreviation	Term
MAC	*Mycobacterium avium* complex
MAR	Missing-at-random
MNAR	missing not at random
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
MPM	modern psychometric methods
NTM	nontuberculous Mycobacteria
PGI-S	Patient Global Impression of Severity
PMR	post-marketing requirement
PRO	Patient-Reported Outcome
PROMIS F-SF 7a	Patient-Reported Outcome Measurement Information System Fatigue-Short Form 7a
PT	preferred term (MedDRA)
QD	once daily
QOL-B	Quality of Life Questionnaire – Bronchiectasis
RMSEA	root mean squared error of approximation
SD	standard deviation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SGRQ	St. George Respiratory Questionnaire
SLR	Standardized Logistic Regression
SOC	system organ class (MedDRA)
TEAE	treatment emergent adverse event
TEAESI	treatment emergent adverse event of special interest
ULN	upper limit of normal
VAP	Validation Analysis Plan
WHO	World Health Organization
WSMC	within-subject meaningful change

2. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for study INS-415.

The reader is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for a subject to complete participation in this study.

The SAP is intended to be in agreement with the protocol. However, the SAP may contain more details or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the CSR.

Relationship of analysis plans

Three complementary statistical analyses plans are developed for this study:

1. The Validation Analysis Plan (VAP) describes the data scope and psychometric validation methods for assessing the properties of the PRO instruments, QoL-B Respiratory and Promise Fatigue. The VAP analyses focus on the primary objectives of this study (Section 3.1). The results from these analyses will be presented and discussed in the Validation Report.
2. SAP (this document) describes the analyses for the secondary and exploratory objectives of the study.
3. DMC SAP describes statistical methods relevant to the safety monitoring committee.

Determination of the PRO Score(s) that will be used to evaluate Arikayce Clinical Benefit

The PRO score(s) that will be used to evaluate the clinical benefit of Arikayce in the context of use in the population of patients newly diagnosed with MAC pulmonary disease will be based on the QOL-B respiratory domain and/or PROMIS Fatigue to create separate scores: one total score for respiratory symptoms and one total score for fatigue symptoms. However, these scores may or may not include all the items from the original domains but may be a subset of those items. No new items will be added as work conducted during the Concept Elicitation Phase of the Qualitative Project indicated that respiratory and fatigue symptoms are the most prevalent and bothersome to patients newly diagnosed with MAC lung disease. The respiratory symptoms that are most prevalent and important to patients are covered by items existing in the Quality of Life-Bronchiectasis (QoL-B) Respiratory Domain (RD); while the fatigue symptoms are covered by items existing in the PROMIS Fatigue instrument.

This final PRO Instrument will be described in the Validation Report.

The analyses of this PRO instrument will be performed as described in Sections:

- 9.3.2 QOL-B Patient-reported Respiratory Symptoms at Month 7

- 9.3.8 Subgroup Analysis
- 10.3 Subjects meeting WSMC
- 11.4 Correlations

Should the PRO score(s) differ in structure or derivation from the original scale based on the empirical evidence presented in the Validation Report the above analyses will be produced post-hoc and will be included in the CSR appendix.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary Objective and Endpoints

The analysis corresponding to the listed objectives in this section are described in the VAP.

Objective	Endpoint
To generate evidence demonstrating the domain specification (via modern psychometric methods), reliability, validity, and responsiveness (within-subject meaningful change) of the PRO endpoints	Findings on psychometric validation optimized and reported for: 1) Cross-sectional validation (modern psychometrics, internal consistency, concurrent validity, and known-groups validity) at Baseline. 2) Test-retest reliability between Screening and Baseline among subjects reporting no change on PGI-S between Screening and Baseline. PGI-S anchors will be PRO specific, with a respiratory and fatigue PGI-S applied to the QOL-B respiratory domain and PROMIS F-SF 7a, respectively. 3) Within-subject meaningful change estimated via anchor-based methods and validated via eCDFs and ePDFs between Baseline and EOS (Month 7).

3.2. Secondary Objectives and Endpoints

To evaluate the effect of each treatment arm (ALIS + background regimen and ELC + background regimen) on the following:

Objective	Endpoint
Culture conversion by Month 6	Proportion of subjects achieving culture conversion by Month 6 (negative cultures for MAC at Month 5 and Month 6)
Patient-reported respiratory symptoms at Month 7	Change from Baseline to Month 7 in respiratory symptom score
Patient-reported fatigue symptoms at Month 7	Change from Baseline to Month 7 in fatigue symptom score

Objective	Endpoint
Time to culture conversion	Time to culture conversion (first of 2 consecutive negative cultures) of Baseline to EOT assessments
Time to first negative culture	Time to first negative culture of Baseline to EOT assessments
MAC isolates with amikacin MIC ≥ 128 μg/mL	Proportion of subjects who develop a MAC isolate with amikacin MIC ≥ 128 μg/mL at more than 1 visit at any timepoint during the study
Recurrence of MAC (relapse)	Proportion of subjects who achieved culture conversion and subsequently have at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits that is the same species and genome as cultured at Screening/Baseline.
Recurrence of MAC (new infection)	Proportion of subjects who achieved culture conversion and subsequently have at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits that is different than cultured at Screening/Baseline (different species or same species but different genome).
Safety and tolerability of ALIS + background regimen	Incidence and severity of AEs and TEAEs and other safety variables (eg, vital signs, physical examination, clinical laboratory values) from Baseline through the EOS

3.3. Exploratory Objectives and Endpoints

To evaluate the effect of each treatment arm (ALIS + background regimen and ELC + background regimen) on the following:

Objective	Endpoint
Patient-reported non-respiratory symptoms at Month 7	Change from Baseline to Month 7 in the QOL-B non-respiratory domains (physical, role, vitality, emotional, social, health perception)
Within-subject meaningful change threshold estimated in respiratory symptoms from Baseline to Month 7	Proportion of subjects meeting the within-subject meaningful change threshold as reflected in PRO changes scores computed from Baseline in patient-reported symptoms
Mean activity and sleep efficiency over time	Longitudinal summary of mean activity and sleep efficiency as measured by Philips Actiwatch Spectrum PRO

4. STUDY DESIGN

4.1. Summary of Study Design

This is a randomized, double-blind, placebo-controlled, active comparator study in eligible subjects with a new diagnosis (initial or subsequent) of MAC lung infection who have not started treatment for their current infection. Subjects will be randomized at Baseline in a 1:1 ratio to receive one of the two treatment regimens: ALIS + background regimen or ELC + background regimen for 6 months. Note that background regimen in this study is defined as AZI+ETH per randomized treatment, and study drug refers to ALIS/ELC, AZI or ETH.

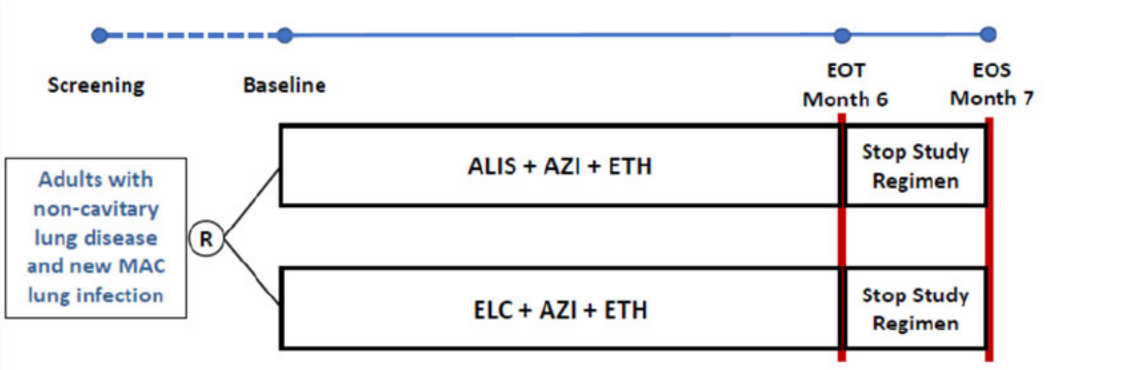
Randomization will be stratified by region (North America, Europe, and Rest of World) and history of MAC lung infection (initial or subsequent). After Baseline, subjects will return to the study site for in-clinic visits at Months 1, 3, 5, 6/EOT, and 7/EOS.

Visits at Months 2 and 4 do not require in-clinic appointments. At these non-in clinic visits, AEs and concomitant medications will be assessed, eDiary data will be collected continually for assessment of study drugs intake, and subjects will be required to produce and ship sputum samples. At the Month 6/EOT visit, subjects will discontinue all study drugs and will be followed for a 1-month off-treatment period, during which medical or non-medical therapies for MAC lung infection should not be given.

At Month 7/EOS, subjects will complete all protocol-specified assessments and the final EOS procedures.

The procedures and assessments conducted at each study visit in the study are provided in Table 4 of the protocol. Please refer to Figure 1 for a schematic diagram of the study design.

Figure 1: Study Design



ALIS = amikacin liposome inhalation suspension; AZI = azithromycin; ELC = empty liposome control; EOS = end of study; EOT = end of treatment; ETH = ethambutol; R = randomization

Subjects who discontinue study drug(s) early are encouraged to stay in the study for continued safety monitoring which begins at EOT and ends 7 months after randomization. The data collected after treatment discontinuation will include all efficacy assessments (in addition to safety) as for those who continue randomized therapy.

4.2. Treatment, Route, Dosage, Treatment Period

Eligible subjects with non-cavitary lung disease with new (initial or subsequent) MAC lung infections who have not started treatment for their current infection and who have signed the ICFs will be randomized and will receive treatment as follows:

- ALIS 590 mg QD + AZI 250 mg QD + ETH 15 mg/kg QD for 6 months, or
- ELC (matching placebo for ALIS) + AZI 250 mg QD + ETH 15 mg/kg QD for 6 months

Treatment

In this study, the term "treatment" or "treatment group" designates the randomization arm to which a subject is assigned, i.e., either ALIS + AZI + ETH or ELC + AZI + ETH.

Treatment Period

The treatment period starts with the first dose of ALIS/ELC, AZI and/or ETH.

The end of treatment (EOT) is defined as the date of the last dose of ALIS/ELC, AZI and/or ETH whichever study drug dose is taken last.

4.3. Sample Size Determination

4.3.1. Power and Sample Size Determination for the Validation Study

Cross-sectional validation will require baseline data from a maximum of 250 subjects to adequately power the planned MPMs. A total of 100 subjects will be enrolled in this study and will be used for this analysis. Additional baseline data from up to the first 150 subjects enrolled in INS-416 study will be used.

Longitudinal validation will require 100 subjects to adequately power the planned within-subject meaningful change methods.

The derivation of these sample sizes and the procedures used to compute power are described below.

Cross-sectional Validation Power and Sample Size

The estimated sample size required to conduct cross-sectional validation of the PRO endpoints within the NTM-MAC population was obtained from a power analysis assuming the PRO will be composed of 10 total items analyzed with 5 response categories each. This power procedure determines the sample size required to detect a domain specification that fits the data acceptably well (Serrano and Iaconangelo, 2019[10]; Serrano and Iaconangelo, 2017[11]). The model fit statistic for which power was computed is the RMSEA. The RMSEA is the primary fit index used in modern psychometric methods for determining the optimal domain structure. This fit assessment is the logical test to power, as the modern psychometric methods require the largest sample sizes of all validation analyses. Therefore, adequately powering modern psychometric methods is key to validation study success. In addition, the precision of all validation analyses subsequent to modern psychometric methods rely on correct domain specification, which itself relies on the RMSEA.

For a 10-item questionnaire, approximately n=250 is required to achieve a power of 0.80 for the RMSEA-based test of acceptable MPM model fit. Therefore, a maximum of 250

subjects are planned for the study cross-sectional validation analyses. These subjects will contribute data at both Screening and Baseline for the purposes of estimated test-retest reliability as well. Longitudinal validation analyses will be conducted on the subset of 100 subjects enrolled into this study.

Longitudinal Validation Power and Sample Size

An empirical power analysis simulation was conducted to evaluate the optimal sample size to adequately characterize culture converter anchor-based within-subject meaningful change in this study.

Inputs to the power analysis simulations were obtained from the MAC subset of the ALIS treated subjects in Insmed Study TR02-112, and simulation conditions considered reflected conservative variation around observed estimates (larger dispersion and smaller magnitudes of effect). The following conditions were used to compute power: magnitudes of effect in change from baseline (6pt, 7pt, 8pt, 9pt, and 12pt change from baseline in converters, and 3 point change from baseline in non-converters); culture converter proportions (50%, 60%, and 70%); proportion data missing at random (MAR, 0%, 5%, 20%, 25%, and 30%); and sample size (n=100, n=120, and n=130). The polyserial correlation between simulated change from baseline in QOL-B respiratory domain and culture conversion varied around the observed estimate of 0.47, ranging from 0.3 to 0.6. Within each unique simulation condition r=1000 replications were generated. Empirical power was computed as the number of replications for which statistically significant differences between converters and non-converters in change from baseline in QOL-B respiratory domain score were observed. For example, if 900 replications demonstrated significant differences using the 2-sided test conducted at α=0.05, then power was 90%.

A total sample size of 100 subjects (50 subjects per treatment arm) will provide at least 80% power for detecting 7 points mean difference in QOL-B respiratory domain response at 1-month post-treatment between subjects achieving culture conversion during the study and those who did not via ANOVA testing. This derivation assumes 50%, 60%, or 70% culture conversion rate, at least 40% polyserial correlation between culture conversion and QOL-B respiratory domain response, and missing data of 0%, 5%, or 20%.

4.4. Randomization

Upon meeting all inclusion/exclusion criteria at baseline visit, subjects will be randomly assigned through IWRS in a 1:1 ratio to either of the treatment groups. The randomization will be stratified by region (North America, Europe, and Rest of World) and history of MAC lung infection (initial or subsequent). Subjects, Investigators, and the Sponsor will be blinded to treatment group assignments and microbiology results throughout the study. In case of subject emergencies, unblinding of the assigned treatment will occur per established procedure.

5. PLANNED ANALYSES

5.1. Validation Analysis

The methods for validation analyses are described in the VAP. The results will be reported separately within the Validation Analysis Report.

Validation analysis include the following:

1. Scoring: Cross-sectional validation (modern psychometrics, internal consistency, concurrent validity, and known-groups validity) at Baseline.
2. Reliability and validity of scores: Test-retest reliability between Screening and Baseline among subjects reporting no change on PGI-S between screening and baseline. PGI-S anchors will be PRO specific, with a respiratory and fatigue PGI-S applied to the QOL-B respiratory domain and PROMIS F-SF 7a, respectively.
3. Responsiveness: Longitudinal analysis - Within-subject meaningful change estimated via anchor-based methods and validated via eCDFs and ePDFs between Baseline and EOS (Month 7).

The analyses for Scoring, Reliability, and Responsiveness require Screening and Baseline data from up to a maximum of 250 subjects (100 subjects from INS-415 study and the first enrolled 150 subjects from INS-416 study). This sample size allows for initiation of RMSEA-based model fit testing with baseline data only (blinded to randomized study groups) from less than 250 subjects; therefore, an attempt will be made when 180 and/or 230 subjects will be enrolled in this study and INS-416 combined. Only if RMSEA-based model fit power testing demonstrates good model fit would cross-sectional validation then proceed. If testing does not indicate good fit at 180 or 230 it would be re-evaluated when 250 subjects are enrolled, which is the maximum planned for cross-sectional validation. RMSEA-based testing ensures the analysis will be performed with sufficient power, voiding any significant impact on the scientific validity of the study. Further, the analysis does not require treatment group assignment, hence will be performed as soon as the data will be available and cleaned, ie, before the unblinding of the INS-415 study. Further details are included in VAP.

The longitudinal analysis requires observed post-baseline data, hence will be performed after data base lock and unblinding of the study.

5.2. Final Analysis

Final analysis is planned to be conducted after data base lock and unblinding of the study.

The final validated PRO instrument will be based on the QOL-B respiratory domain or PROMIS Fatigue but may or may not include all the items from the original scale. Should one or both scales change, certain analyses will be provided on this final PRO Instrument. The change in scales will be provided at the time of Validation Report; hence, the revised analyses if appropriate will be appended to the CSR.

If the number of items used in the PRO scores(s) is a subset of the complete set, the following endpoints and analyses may be revised:

Table 2: List of Endpoints and analyses affected by scoring algorithm change

Endpoint	Analysis	Analysis description included in SAP Section
Patient-reported respiratory symptoms at Month 7	Change from Baseline to Month 7 in respiratory symptom score	Section 9.3.2
	Summaries by timepoint	Section 9.3.2
	Within-subject meaningful change threshold estimated in respiratory symptoms from Baseline to Month 7	Section 10.3
	Subgroup analyses	Section 9.3.8
	Correlations	Section 11.4
Patient-reported fatigue symptoms at Month 7	Change from Baseline to Month 7 in fatigue symptom score	Section 9.3.3
	Summaries by timepoint	Section 9.3.3
	Within-subject meaningful change threshold estimated in respiratory symptoms from Baseline to Month 7	Section 10.3
	Subgroup analyses	Section 9.3.8
	Correlations	Section 11.4

5.3. DMC Monitoring Analysis

Periodic review of data for the purpose of safety will be conducted by the DMC; details are described in a separate DMC charter and DMC SAP, together with details regarding safety summaries and listings. DMC meetings will be held when approximately 25%, 50%, 75%, and 100% of total planned number of subjects in studies INS-415 and INS-416 are randomized. Subsequent meetings will be held approximately every 6 months until completion of the study.

6. ANALYSIS SETS

6.1. ITT Analysis Sets

The ITT analysis set comprises all subjects who were randomized. This set will be analyzed using the treatment to which the subject was randomized.

6.2. Safety Analysis Set

The safety analysis set comprises all subjects who were randomized and received at least 1 dose of ALIS, ELC, AZI or ETH.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1. General

All summaries will be provided by treatment group; efficacy analyses will utilize randomized treatment (ITT analysis set), while safety will use treatments as received (Safety analysis set).

In case of misrandomization to incorrect strata, subjects will be analyzed as collected in CRF.

Methods of cross-sectional analyses and psychometric validation of PRO are described in the VAP.

Descriptive statistics for continuous variables include n, mean, SD, median, minimum, maximum, 1st quartile and 3rd quartile. Summaries of continuous variables that have some values recorded using approximate values (eg, < or >) will use the numeric part of the value in calculations. Listings will present the data in its original format.

Categorical variables will be tabulated by counts and by percentage of subjects in corresponding categories. Footnotes will specify the basis for the percentages. Category including missing assessments will be included if appropriate.

Data from unscheduled visits will not be used in summaries, except for the derivation of baseline and the summary of subjects with an abnormal laboratory value.

Listings corresponding to all summaries in this section will be provided. Listings will also include data from unscheduled visits.

7.2. Multiple Comparisons and Multiplicity

All summaries presented within the scope of this SAP will be descriptive without multiplicity adjustment. Ninety-five percent confidence intervals for estimation of treatment differences and associated p-values will not be adjusted for multiplicity. There is no intention to make inferences based on these statistics, as their value is nominal.

7.3. Baseline Definition

Unless otherwise stated, for the purpose of analysis baseline value is the last non-missing value prior or at the date of the first dose of ALIS/ELC, AZI or ETH, regardless of the visit in which it occurs including unscheduled visits.

Change from baseline will be calculated as:

- Change from baseline = post baseline value – baseline value

Ratio from baseline will be calculated as:

- Ratio from baseline = post baseline value / baseline value

Many assessments are done at Screening and Baseline/Day 1. For summaries, whenever baseline is presented, the above baseline definition is used. That is, the baseline summary presented is in general not the summary of the Baseline/Day 1 visit. Screening values will be listed but not summarized.

Throughout the document Baseline (capital B) refers to the visit Baseline/Day 1; baseline (lower case b) refers to the values derived using the baseline definition above.

The baseline MAC species/genome is the species grown in sputum samples collected at Baseline/Day 1. If Baseline/Day 1 is MAC culture negative or missing, the Screening samples will be taken instead (see Section 9.3.7.1).

Subjects being evaluated in this study have a diagnosis of MAC lung disease, as indicated by an investigator-reported positive MAC culture within 6 months of Screening, and a single sputum sample that is positive for MAC culture at Screening. For the purpose of descriptive summaries at Baseline, if culture assessment is negative at the Baseline visit, the baseline culture status will be regarded as the value at the screening visit.

For the purpose of actigraphy data analysis, baseline will be defined as data recorded in the period Day 8 – Day 14.

7.4. Handling of Missing Data

The handling of missing data and appropriate imputations described in the following sections will be performed after all efforts fail to obtain the data.

If appropriate, retrieved data will be used. A retrieved assessment is one collected after the early discontinuation of ALIS/ELC; a retriever is a subject who stays in the study and continues to provide data after discontinuation of the randomized treatment regimen.

7.4.1. Missing PRO Administrations and Missing Item Responses

Missing individual PRO items will not be imputed. Missing PRO items will be very rare given the ePRO collection procedures.

Domain scores will be calculated as described within the corresponding variable section. In cases when the domain score is derived, derivation will follow the rules specified for missing data handling described within the corresponding efficacy section.

The imputation details of this data are described in Section 9.3.2.2 and Appendix I.

7.4.2. Missing Culture Conversion Assessments

Handling missing microbiological results is described in the protocol Section 8.1 and SAP Section 9.3.1.

Missing data that resulted from early termination of therapy has the same reasons as those described for the PRO. The imputation details of this data are described in Appendix I.

7.4.3. Missing Start and Stop Dates for Prior and Concomitant Medication

The rules to categorize medications as 'Prior' and/ or 'Concomitant' are described in Section 12.14. There is no need to impute missing or partially missing start or stop dates.

7.4.4. Missing Start and Stop Dates for Adverse Events

The rules to categorize AEs to 'TEAE' or 'non-TEAE' are described in Section 12.4. There is no need to impute missing or partially missing start or stop dates.

7.4.5. Missing Dates Drug Interruption

Missing end date of drug interruption will be imputed by date of EOT or EOS whichever comes first.

7.5. Intercurrent Events

The ICEs are defined as post-randomization events that occur after the study intervention has been initiated and which either precludes the observation of the outcome variable or affects its measurement or interpretation. This study identified ICEs as those leading to early ALIS/ELC therapy termination due to death, treatment (ALIS/ELC) related TEAE, use of rescue medication, or lack of efficacy.

When appropriate, efficacy analyses for secondary endpoints will be evaluated taking ICEs into consideration allowing a more precise estimation. Details on handling data after ICE occurred together with justification are provided in Section 9.

7.6. Derived and Transformed Data

7.6.1. Durations

A duration between one date (*date1*) and another later date (*date2*) is calculated using the following formula:

- Duration (days) = *date2* – *date1* + 1
- Duration (weeks) = duration (days) / 7
- Duration (months) = duration (days) / 28
- Duration (years) = duration (days) / 365.25

7.6.2. Study Day

Study Day associated with an event is calculated as the date of the event minus the date of first exposure to ALIS/ELC, ETH, or AZI (whichever is first) plus one (1) if the date of event is on or after the date of first exposure to study treatment.

If the date of event is before the date of first exposure to study treatment, the Study Day will have negative values and is calculated as the date of event minus the date of first exposure to study treatment.

Consequently, there is no Study Day 0.

7.6.3. Off-Treatment Day

The Off-Treatment Day is calculated as the date of event minus the date of last dose of study drugs if the date of event is on or after the date of last dose of study drugs. If the date of event is before the date of last dose of study drugs, Off-Treatment Day is set to missing.

On the date of last exposure to study drugs Off-Treatment Day will be 0.

7.6.4. Multiple Assessments

Unless otherwise stated, if a subject has more than one numeric laboratory record for a specific parameter of interest at a specific visit and/or timepoint for any reason, the average of those specific data at that visit and/or timepoint will be considered in summary tables. Repeated values within a visit or timepoint will be listed individually.

If results are provided from both local and central laboratories, the central assessment will be used for reporting purposes.

7.6.5. Visit Re-labeling

In case of early termination of study, the Month 6/EOT and Month 7/EOS visit will be re-labeled chronologically and stored in variable AVISIT in all visit-based ADaM data sets.

Based on the visit date and the randomization date, AVISIT will be calculated as

Re-labeled visit = (Visit Date – Randomization Date)/ 28*

* rounded to the nearest month

Assessment dates will be compared to the visit date reported on the eCRF form ‘Visit’. If the assessment date is equal to a visit date that belongs to visit which is different from the originally reported visit, then the visit is remapped to the visit reported on the ‘Visit‘ form.

8. STUDY POPULATION SUMMARIES

The ITT analysis set will be used for all study population summaries unless otherwise stated. Summaries for other analyses sets will be provided only if the number of subjects substantially (>10%) differs from the ITT counts. Summaries of the baseline data for assessments also collected after randomization will be presented together with post-randomization data, as appropriate.

8.1. Subjects Disposition

For subjects screened, the number of subjects who are screened, the number of subjects who failed screening, and the reasons for screen failure will be summarized.

Subject disposition will be summarized to present the number of subjects who are randomized, the number and percent of subjects who are randomized and treated, the number and percent of subjects who completed/discontinued from the study or study drug(s) and the reason for discontinuation (including COVID-19). Percentages will be based on the ITT analysis set.

8.2. Demographic and Baseline Characteristics

Demographic and baseline characteristic variables will be summarized. These variables include country, age, sex, ethnicity, race, height, weight, BMI, FEV_1, the stratification variables region (North America, Europe, and Rest of World) and history of MAC lung infection (initial or subsequent), and PROMIS F-SF 7a T-scores.

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg) (baseline value)} / [\text{height (cm)}/100]^2$$

In addition, patient count with MAC infection at baseline (Mycobacteria isolate species (*Mycobacterium avium* complex overall, *M. avium*, *M. intracellulare*), and other speciated and unspeciated MAC) will be provided.

8.3. Protocol Deviations

Deviations from the study protocol will be monitored throughout the conduct of the study. Rules and definitions are included within the study document INS-415/INS-416 Protocol Deviation Management Plan.

Major protocol deviations that affect primary efficacy and safety assessments (as applicable), the safety of a subject or the scientific value of the study will be summarized descriptively.

The PD subtypes will be combined into the following categories:

- GCP: I01, I02, I03, I06, I07, I16
- Safety and Oversight: I05, I11, I12, I13
- Documentation: I08, I09, I10,
- Regulatory compliance: I04, I14
- I/E criteria: P02, P03
- Investigational product/concomitant medications: I15, P04, P05, P06, P09

- Endpoint assessment: P07
- Study procedures: P08, P10
- Other: P13

8.4. Medical History

All medical history will be coded using MedDRA. The incidence of medical history will be summarized using descriptive statistics by SOC and PT. Subjects are counted only once in each SOC and only once in each PT.

8.5. COVID-19 Impact

Potential COVID-19 impact is captured in the eCRF and will be summarized by subject.

Subject disposition summary and listing will include:

- Screen failure related to COVID-19
- Treatment discontinuation related to COVID-19
- Early termination of study related to COVID-19

AE overview table and listings will include:

- AEs that fall into the category of COVID-19 related

Summary table and listing of dose interruption will include:

- Dose interruption related to COVID-19

Summary and listing of protocol deviations will include:

- Protocol deviations due to COVID-19

9. EFFICACY

9.1. General

9.1.1. Reporting Statistics

Nominal p-values will be provided for all efficacy analyses in which differences between groups and 95% CIs are evaluated.

9.1.2. Usage of the covariates in the statistical models

The study was randomized with two stratification strata: history of MAC disease and region (North America, Europe, and Rest of World). The statistical modeling using these categorical variables would imply a total of 12 strata combinations: 2 (treatments) * 2 (history of MAC disease) * 3 (geographical regions). Since the sample size for this study is 100 subjects, it is expected for some strata to have empty cells, resulting in inestimable parameters. Therefore, geographical region is not used in the model for all analyses included in this SAP. Impact of this variable is addressed in the subgroup analyses.

9.2. Primary Endpoint

There is not a single primary endpoint of this study given the objectives of this study. As per Section 3.1 there is a set of psychometric variables that are used to demonstrate the domain specification (via modern psychometric methods), reliability, validity, and responsiveness (within-subject meaningful change) of the PRO instruments. Detailed analysis plan is included in the VAP for the psychometric methods. VAP analysis results will be reported in a separate report (Validation Report).

9.3. Secondary Endpoints

9.3.1. Culture Conversion by Month 6

9.3.1.1. Variable Description

MAC Culture Assessment

Microbiological assessment of sputum specimens is the secondary efficacy measurements in this study.

During the study, subjects are required to provide expectorated or induced sputum samples before dosing with the study drugs. To improve the chance of obtaining an acceptable sputum specimen for culturing, 2 sputum samples will be obtained from each subject at each assessment; subjects will provide 1 sputum sample on the day prior to the scheduled visit, and 1 sputum sample on the day of the visit, both are prior to dosing with study drugs. At Screening, subjects will provide 1 sputum sample on the day of the visit and 1 sputum during the week following the Screening visit. Both sputum samples from each visit will be assayed.

Sputum specimens will be cultured in broth media (liquid) in addition to agar media (solid) and will be held for up to 6 weeks. A negative culture result will not be reported

until after this time has transpired. All samples contaminated by organisms other than MAC will be re-processed and re-cultured once.

MAC culture negative

MAC culture negative is defined as no MAC growth on agar media and broth media in all sputum cultures at a visit. If at least one medium has a negative result, and no medium has a positive result, the MAC culture is negative. If all samples are contaminated, the MAC culture is considered negative. In case of contradictory culture results, ie, one sample positive and the other negative, the visit will be considered to have a positive culture for the purpose of analysis.

Single broth positive timepoints should be considered negative for MAC if preceded by conversion. This must be a single instance of positive broth. Single broth positive timepoints should be considered positive for MAC if preceded by non-conversion. The definition of recurrence supersedes this rule (e.g. if broth positive followed by positive broth consecutively at the next visit, then that meets definition of recurrence),

Culture Conversion

Culture conversion is defined as MAC culture negative at 2 consecutive visits during the treatment period. The conversion status will be reversed by a positive culture after conversion (recurrence). As such, a subject may achieve culture conversion multiple times during the study. The date of conversion is defined by the date of the first of 2 consecutive negative cultures.

The secondary endpoint culture conversion by Month 6 is defined as MAC culture negative at Month 5 and Month 6 with the adjustment for non-productive sputum (described below) and additional rules described in Section 9.3.1.2.1.

Non-productive sputum assessments

If a subject is unable to produce sputum spontaneously, sputum may be induced. If after induction, a subject is still unable to produce sputum despite reasonable efforts, this will be recorded as non-productive at that timepoint.

A non-productive assessment will be considered culture positive if the assessment occurs prior to culture conversion or post recurrence. A non-productive assessment will be considered culture negative if the assessment occurs post culture conversion.

9.3.1.2. Analysis

The endpoint of interest is the proportion of subjects achieving culture conversion by Month 6 as this is the last month of exposure to study medication in this study. The reporting will be presented based on the ITT analysis set and will be provided by randomized treatment group.

The analysis model is the Standardized Logistic Regression (SLR), the model includes response variable, ie conversion status by Month 6 and the following independent variable (stratum at randomization):

- history of MAC lung infection, (initial or subsequent)

The summaries will include:

1. Estimation of group proportions of subjects achieving conversion by Month 6 and difference of these proportions between the treatment groups together with corresponding 95% CIs will utilize the above described SLR model.

   The estimation obtained from SLR will be based on the standardized procedure described in Steingrimsson et al[13] , the SAS macro %Margin, version 2.0 (or later), provided SAS Institute (see SAS note https://support.sas.com/kb/37/228.html) will be used for implementation.

2. Descriptive statistics, ie, number/frequency of subjects with available assessments and conversion status (ie, rules 1 through 4) will be applied as described in Section 9.3.1.2.1.

9.3.1.2.1. Data Handling

For the purpose of the analysis the influence of ICEs (Section 7.5) and the presence of the missing data on the estimation of culture conversion proportion by Month 6 will be taken into consideration.

Culture conversion by Month 6 will be handled by following rules:

1. Data will be adjusted for non-productive visits
2. A subject who dies after randomization will be considered non-converter by Month 6
3. Retrieved sputum assessments will be used in the analysis, ie, collected after early termination of ALIS/ELC (see Section 7.4 for definition)
4. Subjects with a missing assessment at Month 5 or 6 but not both, will be considered converters by Month 6 if they meet all of the following criteria:

- achieved culture conversion (2 consecutive monthly negative sputum cultures) at or before Month 5,
- have negative cultures after conversion with at most 1 missing sputum assessment at or before Month 4,
- have negative culture at Month 7,
- do not have recurrence after conversion.

  Justification for the rule: The protocol defines culture conversion as no MAC growth on agar media and broth media in all sputum cultures at 2 consecutive visits. Month 6 conversion requires both Months 5 and 6 cultures to be negative for MAC (after non-productivity adjustment); if one of them is missing, culture conversion status cannot be determined. However, in the presence of other post-randomization data, in the instances described above this status may be assigned deterministically, consistent with common clinical practices.

5. Data for subjects who complete 6 months of the randomized treatment however conversion status by Month 6 is not available will be imputed based on the observed status distribution from the subjects who completed 6 months of randomized treatment (ALIS/ELC, AZI, and ETH), have Month 6 conversion

status determined, and were randomized to the same treatment group. This approach is consistent with MAR approach imputation.

6. When retrieved assessments are unavailable or #4 does not provide conversion status by Month 6, the missing Month 6 conversion status will be imputed as follows:

- For subjects experiencing ICE (other than death), their missing Month 6 conversion status will be imputed based on the retrieved Month 6 conversion distribution from the subjects experiencing ICE (retrievers). MNAR imputation of the data for those subjects experiencing ICE is applied.

  Justification for the rule: In most cases, physicians caring for patients discontinuing ALIS/ELC due to an ICE will elect to continue AZI and ETH alone or provide an alternative regimen in order to complete an adequate period of treatment for MAC lung infection. In case of an AE leading to ICE, treatment options for MAC lung disease known to be efficacious other than (at a minimum) the combination of a macrolide plus ethambutol already provided in the study are limited. Furthermore, for ICE patients requiring "rescue therapy" as defined in protocol Section 5.2.2 (ie, a change from randomized treatment due to progression of MAC lung infection), these patients are failing initial course of therapy and should be considered refractory; recommended treatment in that case would be the addition of ALIS – which may or may not have been the cause of the ICE. Therefore, subjects experiencing an ICE are expected to have a microbiologically worse outcome due to limited treatment options following the ICE, and imputation of PROs to the retriever distribution is more representative of their clinical outcome.

- For subjects not experiencing ICE, their missing Month 6 conversion status will be imputed based on the observed status distribution from the subjects who completed 6 months of randomized treatment, have Month 6 conversion status determined, and were randomized to the same treatment group. This approach is consistent with MAR approach imputation.

The ELC treatment group (including retriever) will be used instead if the ICE retriever subgroup is too small to allow imputations as described above. The decision as to which group will be used in the imputation will be determined prior to unblinding at the blinded data review meeting.

Imputation details are included in the Appendix I.

9.3.2. QOL-B Patient-reported Respiratory Symptoms at Month 7

9.3.2.1. Variable Description

The QOL-B is a self-administered, reported outcome questionnaire used to assess symptoms, functioning, and health related quality of life in adults with non-CF bronchiectasis (Quittner, 2015[8]). It measures outcomes over a recall period of 1 week. The questionnaire contains 37 items on 8 scales (physical, role, vitality, emotional, social, treatment burden, health perception, and respiratory). There is no overall total score combining all domains of QOL-B.

Appendix A shows the questionnaire and how the data are captured in the eCRF.

Item coding

Each of the 37 items is scored from 1 to 4 with higher scores representing fewer symptoms or better functioning and quality of life.

Before calculating the scale scores, the following preparations are necessary:

- If item 32 = 00 (Green with traces of blood) then item 32 = 1
- If item 32 = 0 (Don't know) then item 32 is set to missing
- If item 19 = 5 (Doesn't apply) then item 19 is set to missing

Scale scores

Each of the 8 domain scores is standardized on a 0 to 100-point scale with higher scores representing fewer symptoms or better functioning and quality of life. Positive change from baseline indicates improvement (post therapy score – baseline score > 0).

Scale scores are derived from a subset of items and calculated by

$$scale\ score = \frac{mean\ of\ responses - 1}{3} * 100.$$

If the responses are missing for more than half of the items in a scale, the score for that scale should not be calculated.

Contributing items:

- Physical Functioning Domain (5 items): 1, 2, 3, 4, 16
- Role Functioning Domain (5 items): 17, 20, 25, 27, 28
- Vitality Domain (3 items): 6, 8, 9
- Emotional Functioning Domain (4 items): 7, 10, 11, 23
- Social Functioning Domain (4 items): 18, 19, 22, 26
- Treatment Burden Domain (3 items): 12, 13, 14
- Health Perceptions Domain (4 items): 5, 15, 21, 24
- Respiratory Symptoms Domain (9 items): 29 to 37

The secondary endpoint of interest is the change from baseline to Month 7 in the respiratory symptom domain score. Other domains are exploratory.

9.3.2.2. Analysis

The analysis of change from baseline to Month 7 in respiratory symptom score (as assessed by QOL-B) will be summarized based on subjects in the ITT analysis set by treatment group.

The analysis model is the ANCOVA, the model includes response variable, ie, change from baseline to Month 7 and the following independent variables:

- history of MAC lung infection, (initial or subsequent)

- baseline QOL-B Respiratory domain score

The regression coefficient for treatment group in the ANCOVA is equal to the estimated population-level average treatment effect of $\mu_{ALIS}-\mu_{ELC;}$ this estimate will be used in Wald tests deriving p-value for the difference between the treatments groups. The p-value is nominal as the study is not a hypothesis testing and further is not powered for this comparison.

The summaries will include:

1. LS-mean of change from baseline to Month 7, differences of LS-mean changes from baseline (ALIS + background regimen minus ELC + background regimen) estimates and corresponding 95% CIs derived from ANCOVA model.
2. Descriptive statistics by timepoint with corresponding change from baseline.

9.3.2.2.1. Data Handling

For the purpose of the analysis the influence of ICEs and the presence of the missing data on the estimation of change from baseline to Month 7 PRO means will be taken into consideration. The ICEs are defined as post-randomization events leading to early ALIS/ELC therapy termination due to death, ALIS/ELC-related TEAE, use of rescue medication, or lack of efficacy.

Change from baseline to Month 7 will incorporate the following considerations:

1. A subject who dies after randomization will be assigned the worst observed change score in the entire sample as the change from baseline to Month 7
2. Retrieved Month 7 assessments will be used in the analysis, ie, collected after early termination of ALIS/ELC (see Section 7.4 for definition)
3. Data for subjects who complete 6 months of the randomized treatment however their Month 7 PRO is not available will be imputed based on the observed status distribution from the subjects who completed 6 months of randomized treatment (ALIS/ELC, AZI and ETH), have Month 7 available, and were randomized to the same treatment group. This approach is consistent with MAR approach.
4. When retrieved assessments are unavailable the missing change from baseline to Month 7 will be imputed as follows:

- For subjects experiencing ICEs other than death, their missing Month 7 PRO will be imputed based on the retrieved assessment distribution from those retrievers who experienced ICE and are exposed to an altered treatment regimen after their ICEs. MNAR imputation of the data for those subjects experiencing ICE is applied.

  Justification for usage of retrievers' data is included in Section 9.3.1.2.1.

- For subjects not experiencing ICE, their missing Month 7 PRO data will be imputed based on the observed data distribution from the subjects who completed 6 months of randomized therapy (ALIS/ELC, AZI and ETH), have Month 7 PRO data assessment available, and are randomized to the same treatment group. This approach is consistent with Missing-at-Random (MAR) approach.

Imputation details are included in Appendix I.

The ELC treatment group will be used instead if the ICE retriever subgroup is too small to allow imputations as described above. The decision as to which group will be used in the imputation will be determined prior to unblinding at the data review meeting.

The results of the analyses for each imputation will be combined using Rubin's rule.

9.3.2.3. Sensitivity Analysis

As sensitivity analysis, a different rule for obtaining the combined p-value from the analysis of the multiple imputation will be applied.

Wald Chi-Square statistics will be calculated and will be combined using Rubin's rule result in a single combined p-value.

9.3.3. Patient-reported Fatigue Symptoms at Month 7 - PROMIS Fatigue

9.3.3.1. Variable Description

The PROMIS F-SF 7a is a self-administered questionnaire assessing a range of self-reported symptoms over the past 7 days, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles (Ameringer, 2016[1]). Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities over 7 items.

Response options are on a 5-point Likert scale, ranging from 1=never to 5=always.

Item coding

Item FATIMP40 must be recoded from (1=never, ...,5=always) to (1=always, ..., 5=never) as shown in Appendix B before any further scoring.

Raw score

The raw score is the sum of responses to all 7 questions, ranging from 7 to 35. Lower values represent a better state of health.

T-score

The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10.

Table 3: Scoring table PROMIS F-SF 7a

Raw Score	T-score	Raw Score	T-score	Raw Score	T-score
7	29.4	17	52.2	27	66.3
8	33.4	18	53.7	28	67.8
9	36.9	19	55.1	29	69.4
10	39.6	20	56.4	30	71.1
11	41.9	21	57.8	31	72.9
12	43.9	22	59.2	32	74.8
13	45.8	23	60.6	33	77.1
14	47.6	24	62.0	34	79.8

15	49.2	25	63.4	35	83.2
16	50.8	26	64.8		

9.3.3.2. Analysis

Change from baseline to Month 7 in fatigue symptom raw score (as assessed by PROMIS F-SF 7a) will be analyzed similarly to QOL-B respiratory symptoms domain, see Section 9.3.2.2 for details.

Depending on the outcome of the Validation Report it is possible that the scoring algorithm will change, in such case an analysis based on the modified scoring algorithm will be provided.

9.3.4. Time to Culture Conversion

9.3.4.1. Variable Description

Time to culture conversion is the number of months from the date of first dose of study drugs to the date of the first culture conversion. For the purpose of this analysis, naming convention will be adopted according to the first of the two cultures being negative. For example, culture conversion at Month 3 will require Month 3 and Month 4 cultures to be negative. This definition was adopted since the first culture being negative is an indication of clinical improvement.

Time to culture conversion (months) =

(date of culture conversion – date of first dose of drug intake +1) / 28*

* rounded to the nearest month

Time to conversion will be set to number of months between first study drug(s) intake and date of the first negative culture (in the sequence of the two negative). A subject who died will be considered censored at the last visit with available culture assessment.

Subjects without conversion are considered censored. Time of censoring is set to the last visit with available culture assessment up to and including Month 6.

It should be noted that the definition of culture conversion at Month 1 through Month 6 differ from the definition of culture conversion by Month 6 (Section 9.3.1.1). Time to conversion evaluates the specific timepoint at each culture conversion is achieved. Culture conversion by Month 6 evaluates the cumulative culture status up to and including Month 6.

Cumulative conversion summary for Culture Conversion by Month 6

In addition, an analysis will be performed to include Month 1 through Month 5 cumulative conversion summary. Denominator for this cumulative analysis is number of subjects who converted by Month 6 (rules 1 through 4 will be applied as described in Section 9.3.1.2.1).

Cumulative conversion summary for Culture Conversion by Month 7

An analysis will be performed to include Month 1 through Month 6 cumulative conversion summary. Denominator for this cumulative analysis is number of subjects who converted by Month 7 (rules will be applied as described in Section 11.3).

9.3.4.2. Analysis

Unless otherwise stated analysis of time to culture conversion will be summarized as follows:

1. Basic statistics of time to conversion
2. Number of observations, number of censored observations, number at risk (by visit)
3. Hazard ratio (ALIS + background regimen: ELC + background regimen) and corresponding 95% CIs,
4. Kaplan-Meier plot will be provided
5. A Cox regression model will be applied to calculate the hazard ratio. The model includes effects for treatment and stratification variable (history of MAC lung infection, initial or subsequent).

9.3.5. Time to First Negative Culture

9.3.5.1. Variable Description

Time to first negative culture is the number of months from the date of first dose of study drug(s) to the date of first MAC culture negative post-baseline.

Time to first negative culture (months) =

(date of first MAC culture negative – date of first dose of study drug(s) +1) / 28*

* rounded to the nearest month

Months 1 through Month 7 will be presented. Subjects without MAC culture negative are considered censored. Time of censoring is set to the last visit with available culture assessment up to and including Month 7.

9.3.5.2. Analysis

The same statistics will be presented as described in Section 9.3.4.2.

9.3.6. Microbiology Assessment

Mycobacteria isolate species (*Mycobacterium avium* complex overall, *M. avium, M. intracellulare*, and other speciated and unspeciated MAC) are the variables of interest.

Drug susceptibility of MAC treatment will also be presented.

MIC (µg/mL) is reported in powers of 2, eg, 0.125 = 2^{-3}, 0.25 = 2^{-2}, ... , 64 = 2^{6}, etc. Therefore, the values that may appear in this table are 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 and >128. The MIC will be tabulated for each reported MIC value including any values not reported between the minimum and maximum values.

If there are multiple assessments collected for MIC assessment for one visit, the maximum MIC value will be used.

All variables will be tabulated by treatment (individual and overall) at each timepoint.

The denominator for percentages will be the number of subjects with available data.

9.3.6.1. MAC isolates with clarithromycin MIC ≥ 32 µg/mL

Drug susceptibility to macrolide (ie. AZI) is based on clarithromycin MICs and will be categorized as follows based on Clinical and Laboratory Standards Institute interpretive criteria (Clinical and Laboratory Standards Institute Guideline M24, 2018):

- Sensitive: MIC ≤ 8 µg/mL
- Intermediate: MIC = 16 µg/mL
- Resistant: MIC ≥ 32 µg/mL

For clarithromycin, MICs will be reported up to 32 µg/mL. Values above 32 µg/mL will be reported as > 32 µg/mL.

For each timepoint and, additionally, the maximum MIC for each subject (Month 1 to Month 6), the following summary statistics will be calculated:

- Number and percent of subjects per reported MIC value
- Number and percent of subjects per category indicating resistance: Sensitive, Intermediate, Resistant
- Mean, range, MIC_{50}, MIC_{90}
- Change from baseline (ratio of geometric means)
- Number of subjects with change from baseline ≥ 4 fold

MIC_{50} and MIC_{90} are the antibiotic concentrations required to inhibit growth of 50% and 90% of the isolates, respectively. This can be calculated as 50th-percentile (ie, median) and 90th percentile in SAS using the percentile definition 3 (PCTLDEF=3).

9.3.6.2. MAC isolates with amikacin MIC ≥ 128 µg/mL

Drug susceptibility to amikacin will be reported as described for macrolide in Section 9.3.6.1, with the following deviation:

For amikacin, MICs will be reported up to 128 µg/mL. Values above 128 µg/mL will be reported as > 128 µg/mL.

The breakpoints for inhaled liposomal amikacin are

- Sensitive: MIC ≤ 64 µg/mL
- Resistant: MIC ≥ 128 µg/mL

The summaries of this secondary endpoint will include the number and percentage of subjects in each category (subjects who developed a resistance vs subject who did not develop a resistance) will be presented by treatment group.

Number of subjects who developed a resistance will be plotted over time by timepoint and cumulative over time.

9.3.7. Recurrence

9.3.7.1. Variable Description

Baseline MAC species/genome

The baseline MAC species/genome is the species grown in sputum samples collected at Baseline/Day 1. If Baseline/Day 1 is MAC culture negative or missing, the Screening samples will be taken instead. Screening samples are MAC culture positive, as only subjects with MAC culture positive at Screening are included in the study. If 2 different species/genomes were cultured at baseline, both are considered the baseline MAC species/genome.

Recurrence: Relapse

A relapse is defined as a positive culture that is the **same** species and genome as cultured at baseline subsequent to culture conversion.

If more than one species/genome are found, the subject shows a relapse if any of the cultures match the species/genome(s) at baseline.

The positive culture is defined as at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits. Missing MAC culture assessments which are imputed to positive do not contribute to recurrence.

Note: The definition of positive culture that establishes recurrence is different from the definition of MAC culture positive used for culture conversion.

Recurrence: New MAC Infection

A new MAC infection is defined as a positive culture that is **different** than cultured at baseline (different species, or same species but different genome) subsequent to culture conversion.

If more than one species/genome are found, at least one of the species/genomes must be different than the baseline species/genome(s).

The positive culture is defined as at least 1 positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits.

If a subject shows both relapse and new MAC infection at the same timepoint, relapse is counted for this timepoint only.

9.3.7.2. Analysis

The proportion of subjects who had relapse, and the proportion of subjects with new MAC infection at any timepoint during the study and treatment will be analyzed. Recurrence will be analyzed at the subject level and by timepoint (Month 3 to Month 7).

Number of subjects and percentages will be provided. The denominator is always the respective number of subjects at risk, ie, subjects with culture conversion.

9.3.8. Subgroup Analysis

Treatment effect across major subgroups on the QOL-B Respiratory Symptoms Month 7, PROMIS Fatigue Month 7, and Conversion by Month 6 will be summarized. Subgroup factors are shown in the list below:

- Age: < 65 years, ≥ 65 years
- Gender: Female, Male
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White (races with small counts may be excluded from summaries)
- Stratification variable 'History of MAC lung infection': initial, subsequent
- Stratification variable 'Region': North America, Europe, and Rest of World
- MAC infection at baseline: Mycobacteria isolate species (*Mycobacterium avium* complex overall, *M. avium*, *M. intracellulare*), and other speciated and unspeciated MAC)

The microbiological assessment analysis (MIC and susceptibility) will be summarized for the following subgroups:

- Stratification variable 'Region': North America, Europe, and Rest of World
- MAC infection at baseline: Mycobacteria isolate species (*Mycobacterium avium* complex overall, *M. avium*, *M. intracellulare*), and other speciated and unspeciated MAC)

Subgroup analysis will use the same analytical approach as in the secondary endpoint analyses. Statistical modeling will not include history of MAC lung infection as covariate. Plots will not be generated for subgroups.

10. EXPLORATORY OBJECTIVES

10.1. Analysis

Unless otherwise stated, all summaries pertaining to exploratory endpoints will utilize available data. Summaries will be presented by treatment group and by visit, as appropriate.

10.2. QOL-B Patient-reported Non-respiratory Symptoms

10.2.1. Variable Description

The non-respiratory symptoms domain from QOL-B are

- Physical Functioning Domain
- Role Functioning Domain
- Vitality Domain
- Emotional Functioning Domain
- Social Functioning Domain
- Health Perceptions Domain

Derivations of domains are described in Section 9.3.2.1.

10.2.2. Analysis

Endpoint: Change from baseline to Month 7 in the QOL-B non-respiratory domains

Timepoint: Change between baseline and Month 7

Type of endpoint: Continuous

Summaries will include:

1. Basic statistics of actual values and change from baseline
2. LS-mean of change from baseline, differences of LS-mean changes from baseline (ALIS + background regimen – ELC + background regimen) estimates and corresponding 95% CIs derived from ANCOVA model.

The ANCOVA model will include change from baseline as response variable and treatment, baseline value, and history of MAC lung infection (initial or subsequent) as independent variables.

The basic summaries will be also provided for all other timepoints.

10.3. Subjects meeting WSMC

10.3.1. Variable Description

Within-subject meaningful change (WSMC) from baseline to Month 7 is one threshold on the QOL-B Respiratory Symptoms Domain Score and one threshold on the PROMIS

Fatigue Score and their estimation is described in the VAP. The thresholds will be provided after unblinding of the study and will be provided exclusively for the revised scales, therefore this analysis will be included in the CSR appendix.

The WSMC threshold values will be used to categorize subjects into two categories at Month 7: subjects meeting the criteria of change from baseline to Month 7 meeting or exceeding (in the improved direction) the threshold or not.

10.3.2. Analysis

Endpoint: Proportion of subjects meeting the within-subject meaningful change threshold as reflected in PRO changes scores in patient-reported symptoms (as assessed by QOL-B Respiratory Symptoms domain and PROMIS F-SF 7a)

Timepoint: Change between baseline and Month 7

Type of endpoint: Categorical

Summaries will include:

1. Basic summary statistics: number of subjects in each category
2. Difference of proportions (ALIS + background regimen – ELC + background regimen)

   Estimation of proportions and differences of proportions together with corresponding 95% CIs will utilize SLR of the proportions adjusted for stratification variable (history of MAC lung infection, initial or subsequent)

The estimation obtained from SLR will be based on the standardized procedure described in Steingrimsson et al[13], the SAS macro %Margin, version 2.0 (or later), provided SAS Institute (see SAS note https://support.sas.com/kb/37/228.html) will be used for implementation.

Basic summaries will be performed on the observed data (including retrieved data after ALIS/ELC discontinuation), while inferential summaries (SLR) on the imputed. Specifically, for subjects with imputed QOL-B Respiratory Symptoms score data, change from baseline values will be averaged across 50 available imputations. For PROMIS Fatigue, additionally, averaged values will be rounded to the nearest integer. This method will ensure consistency between data usage in this and anchor-based analysis.

10.4. Actigraphy

10.4.1. Variable Description

The Philips Actiwatch Spectrum PRO actigraphy device resembles a wristwatch and senses the activity of the wearer. It is to be worn continuously by the subject throughout the duration of the study. It is water-resistant and does not need to be removed for bathing. The data collected should be downloaded at each in-clinic visit or during a home care visit (if applicable).

The data are collected continuously by the device and processed by Philips proprietary validated algorithms to derive daily values. Data are collected from visit Day 1 until EOS.

The following variables will be summarized by week using descriptive statistics:

- Total activity count
- Maximal activity count
- Daily percent of mobile time (%)
- Total night sleeping time, TNST (minutes)
- Sleep efficiency (%)

  Sleep efficiency is defined as the ratio of TNST and time in bed.
- Duration nocturnal sleep bouts, DNSB (minutes)

  Average duration of nocturnal sleeping bouts during time in bed. A higher DNSB indicates longer sleeping bouts and, in turn, less nocturnal sleeping disturbances.
- Wake after sleep onset, WASO (minutes)

  Time spent awake during time in bed after the first nocturnal sleep onset.
- Total day sleeping time, TDST (minutes)
- Number of daytime sleep bouts, NDSB

  Number of daytime sleeping bouts indicates how many naps a patient takes during the day.
- Duration daytime sleep bouts, DDSB (minutes)

  Average duration of daytime sleeping bouts during the day. A higher DDSB indicates longer naps.
- Fragmentation index (%)

  An index of restlessness throughout the rest period. It is the sum of percent mobile and percent one-minute immobile bouts for the given interval.

For each of the variables above weekly scores will be computed. A weekly score is computed for a subject if at least 4 daily scores are available for a week.

10.4.2. Analysis

Descriptive summary for the activity and sleep variables will be performed for each week per treatment group. The following will be presented from baseline to Month 7:

- The number and percentage of subjects with data recorded.
- Descriptive statistics (mean, median, standard deviation, first and third quartiles, skewness, minimum and maximum).

- Descriptive statistics for change from baseline to each post-baseline week. The denominator is the number of subjects in the study in the corresponding week.
- A graphical representation will be also provided as timeseries showing weekly mean and weekly mean change from baseline (across patients).

10.5. Subgroup Analysis

Subgroup analyses will be performed on the following:

1. QOL-B non-respiratory symptoms Month 7
2. Subjects meeting WSMC QOL-B Month 7
3. Subjects meeting WSMC PROMIS Fatigue Month 7

Subgroup factors are shown in the list below:

- Age: < 65 years, ≥ 65 years
- Gender: Female, Male
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White (races with small counts might be excluded from summaries)
- Stratification variable 'History of MAC lung infection': initial, subsequent
- Stratification variable 'Region': North America, Europe, and Rest of World
- MAC infection at baseline: Mycobacteria isolate species (*Mycobacterium avium* complex overall, *M. avium*, *M. intracellulare*), and other speciated and unspeciated MAC)

Subgroup analysis will use the same analytical approach as the main analysis. Statistical modeling will not include history of MAC lung infection as covariate.

11. OTHER EFFICACY ASSESSMENTS

11.1. Patient-Reported Outcomes

11.1.1. EXACT®

The EXACT PRO was developed and qualified for use in characterizing COPD clinical endpoints (Jones, 2011[2]; Leidy, 2010[6]; Leidy, 2011[5]; US FDA, 2013[15]). Several of the concepts assessed by the EXACT are relevant to characterizing the symptomatic phenomena expected within bronchiectasis. These include, but are not limited to, dyspnea and fatigue. The EXACT total score measures acute, sustained, and worsening signs and symptoms exceeding subject-specific expected variability. The EXACT PRO is composed of 14 items from which a total score is generated. Domains assessed by the EXACT PRO include dyspnea, cough and sputum production, chest symptoms, difficulty expectorating, fatigue, sleep disturbance, and fear or concern.

If missing values occur for individual items, the scores cannot be calculated and should be set to missing.

EXACT Total Score

A raw summed score is derived as the sum of the item-level raw scores of the 14 EXACT items (see Appendix C).

For each raw summed score, the corresponding EXACT total score is assigned (see Table 4) The EXACT total score has a theoretical range of 0 to 100, with higher values indicating a more severe condition. Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

For the purpose of analysis, if an EXACT total score is 0 it will be changed to missing. This scoring rule is based on previous validation work demonstrating that moderate-to-severe COPD patients will experience symptom(s) each day, and a score of 0 on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s).

Domain scores

Three respiratory symptom domains are also embedded within the EXACT measure: Breathlessness, Cough & Sputum, and Chest Symptoms.

To compute domain scores, compute the raw domain score as the sum of the contributing domains first.

Item assignments to domains are as follows. Please note that items 4, 12, 13, and 14 do not correspond to a domain score and are not used in domain-specific analyses.

- Breathlessness: Items 7, 8, 9, 10, and 11
- Cough & Sputum: Items 2 and 3
- Chest Symptoms: Items 1, 5, and 6

For each raw domain score, the corresponding EXACT Domain score from Table 5 is assigned. The EXACT Domain score has a theoretical range of 0 to 100, with higher

values indicating a more severe condition. Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

Table 4: Raw Summed Score to Scale Score Conversion Table for EXACT Total Score

Raw Summed Score	EXACT Total Score	Raw Summed Score	EXACT Total Score
0	0	26	50
1	8	27	51
2	13	28	52
3	17	29	53
4	20	30	54
5	23	31	55
6	25	32	57
7	27	33	58
8	28	34	59
9	30	35	60
10	31	36	61
11	33	37	63
12	34	38	64
13	36	39	65
14	37	40	67
15	38	41	68
16	39	42	70
17	40	43	72
18	41	44	73
19	42	45	75
20	43	46	77
21	44	47	80
22	46	48	83
23	47	49	87
24	48	50	92
25	49	51	100

Table 5: Raw Summed Score to Scale Score Conversion Table for EXACT Domains

Domain Raw Summed Score	Breathlessness Domain Score	Cough & Sputum Domain Score	Chest Symptoms Domain Score
0	0	0	0
1	11	13	12
2	19	25	23
3	25	39	31
4	30	56	38
5	34	72	45
6	38	86	52
7	42	100	58
8	45		65
9	48		72
10	52		79
11	56		88
12	60		100

Domain Raw Summed Score	Breathlessness Domain Score	Cough & Sputum Domain Score	Chest Symptoms Domain Score
13	65		
14	71		
15	78		
16	87		
17	100		

11.1.2. EXACT RS™

The E-RS is an 11-item subset of the EXACT PRO assessing exacerbations of respiratory symptoms (Leidy, 2014a[4]; Leidy, 2014b[5]).

If missing values occur for individual items, the scores cannot be calculated and should be set to missing.

RS-Total Score

The RS-Total score is the sum of the individual raw item scores (item 1 to item 11) of the EXACT PRO (see Appendix C). Scores range from 0 to 40. Higher values indicate a more severe condition. Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

E-RS: COPD Subscale Scores

For each subscale, the sum of the item-level scores across the items comprising the scale is calculated.

- RS-Breathlessness: Items 7, 8, 9, 10, 11 (score range 0–17)
- RS-Cough & Sputum: Items 2, 3, 4 (score range 0–11)
- RS-Chest Symptoms: Items 1, 5, 6 (score range 0–12)

If the EXACT total score is 0, the RS-Total Score and Subscale Scores will be set to missing.

11.1.3. SGRQ

The SGRQ is a self-administered instrument for the assessment of overall health, daily life, and perceived well-being among individuals with obstructive airway disease (Jones, 1992[3]). The instrument consists of 50 items with 76 weighted responses grouped into a set of 17 questions. The items are divided into 2 parts and 3 categories: symptom, activity, and impact. Part 1 (symptom component) assesses an individual's perception of their recent respiratory problems. Part 1 evaluates frequency and severity of symptoms including cough, sputum production, wheezing, breathlessness, and the duration and frequency of attacks of breathlessness and wheezing. Part 2 (activity and impact components) addresses individuals' current state.

The responses to all questions must be mapped to weights as shown in Appendix D and Appendix E.

The component scores are derived from the summed weights of the contributing questions (see below). After summation, the summed weights are normalized by the maximum possible sum of weights for each component.

$$Score = 100 * \frac{Summed\ weights\ of\ responses\ in\ that\ component}{Maximum\ possible\ weights\ of\ responses\ in\ that\ component}$$

If a response is missing, the weight of this response will not be counted in the denominator, ie., in the *Maximum possible weight of responses in that component*.

The questionnaire contains questions allowing multiple responses. The manual refers to them as 'questions' (question 11-16), the eCRF calls them 'Sections' (Section 2-7). Consistent with the instrument's manual, the term 'question' is used below.

Lower values for the component scores indicate a better state of health. Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

Symptoms component

This is calculated from the summed weights for the responses to questions 1-8. The maximum possible sum of weights is 662.5. The Symptoms component will tolerate a maximum of 2 missed responses.

If the subject had no severe attack in the past 4 weeks (ie, question 5 = "none of the time"), question 6 cannot be answered. In this case, question 6 has a weight of 0 and is not considered missing.

Activity component

This is calculated from the summed weights for the positive responses to questions 11 and 15. As these questions are multiple choice, there is a total number of 16 responses in this component. The maximum possible sum of weights is 1209.1. The Activity component will tolerate a maximum of 4 missed responses.

Impacts component

This is calculated from the summed weights for the positive responses to questions 9, 10, 12-14, and 16-17. As questions 12-14 and 16 are multiple choice, there is a total number of 26 responses in this component. The maximum possible sum of weights is 2117.8. The Impacts component will tolerate a maximum of 6 missed responses.

If the subject did not receive respiratory treatment, question 14 cannot be answered. In this case, all responses to question 14 are considered FALSE even if they are missing on the eCRF. The responses are not missing for the calculation of the component score.

If the subject never held a job, question 10 cannot be answered. In this case, the response should be missing and will be considered missing for the component score.

Total score

This is calculated from the summed weight of all responses in the questionnaire. The maximum possible sum of weights is 3989.4. The total score will be calculated only if all component scores are calculated.

11.1.4. FACIT-Fatigue

The FACIT-Fatigue Scale is a short, 13-item, easy to administer, tool measuring an individual's level of fatigue during their usual daily activities during the past week (Smith, 2010[12]). FACIT-Fatigue is routinely administered in studies of respiratory disease populations for accurately evaluating the common sequelae of fatigue.

The FACIT-Fatigue score ranges from 0 to 52, with higher scores indicating a better quality of life. Positive change from baseline indicates improvement (post therapy score – baseline score > 0).

Item-level reversal

All item values except An5 and An7 must be reversed before further derivations (see Appendix F). The coding must be changed to show 0 = 'Very much' to 4 = 'Not at all'.

Fatigue Subscale Score

The Fatigue subscale score is the sum of the item scores. Missing items will be replaced by the mean of the answered items:

$$Fatigue\ subscale\ score = \frac{Sum\ of\ item\ scores}{Number\ of\ items\ answered} * 13$$

If less than 7 items are answered the subscale score is set to missing.

11.1.5. Analysis of PRO Scores

PRO scores will summarize available data. Summaries will be presented by treatment group and by timepoint, as follows. Summaries will include:

1. Basic statistics of actual values and change from baseline to all protocol-specified timepoints.
2. LS-mean of change from baseline to Month 7, differences of LS-mean changes from baseline (ALIS + background regimen – ELC + background regimen) estimates and corresponding 95% CIs derived from ANCOVA model. The ANCOVA model will include change from baseline as response variable and treatment, baseline value, and history of MAC lung infection (initial or subsequent) as independent variables.

The following PRO scores will be summarized:

EXACT (see Section 11.1.1)

- EXACT Total score
- Breathlessness domain score
- Cough & Sputum domain score
- Chest Symptoms domain score

EXACT-RS (see Section 11.1.2)

- RS-Total score
- RS-Breathlessness subscale score

- RS-Cough & Sputum subscale score
- RS-Chest Symptoms subscale score

SGRQ (see Section 11.1.3)

- Total score
- Symptom component score
- Activity component score
- Impact component score

FACIT – Fatigue Scale (see Section 11.1.4)

- Fatigue subscale score

11.2. PGI-S

11.2.1. PGI-S Respiratory

The PGI-S Respiratory score is a categorical rating of symptom severity. The scale ranges from 1 = not at all to 5 = extremely severe (Appendix G). Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

11.2.2. PGI-S Fatigue

The PGI-S Fatigue score is a categorical rating of symptom severity. The scale ranges from 1 = not at all to 5 = extremely severe (Appendix G). Negative change from baseline indicates improvement (post therapy score – baseline score < 0).

11.2.2.1. Analysis of PGI-S Scores

Change from baseline to Month 7 in PGI-S scores will be analyzed similarly to QOL-B respiratory domain, see Section 9.3.2.2 for details.

Categorical Analysis

The following categories for change from baseline will be defined:

- Very much better if change from baseline = -4
- Much better if change from baseline = -3
- Better if change from baseline = -2
- Somewhat better if change from baseline = -1
- No changed if change from baseline = 0
- Somewhat worse if change from baseline = 1
- Worse if change from baseline = 2
- Much worse if change from baseline =3
- Very much worse if change from baseline = -4

In addition, the following simplified categories for change from baseline will be defined:

- Improved (Very much better / Much better / Better / Somewhat better) if change from baseline <= -1
- No change if change from baseline = 0
- Worse (Very much worse / Much worse / Worse / Somewhat worse) if change from baseline >=1

Within-subject change from baseline to Month 7 are summarized as follows:

- Proportion of subjects in each PGI-S category for change from baseline to Month 7.
- Proportion of subjects in each PGI-S simplified category (Improved/No change/Worsen) for change from baseline to Month 7 (<=-1, 0, >=1) by treatment group and pooled.
- Between treatment groups comparison of the proportion of subjects in PGI-S Improved simplified category (i.e., change from baseline to Month 7 <= -1) using Cochran-Mantel-Haenszel test stratified by history of MAC lung infection (initial or subsequent).

For the purpose of this analysis, PRO data for subjects with missing data, imputations of change from baseline values will be averaged across 50 available imputations and rounded to the nearest integer to obtain a single value per subject.

11.3. Culture Conversion by Month 7

The endpoint of interest is the proportion of subjects achieving culture conversion by Month 7. The reporting will be presented based on the ITT analysis set and will be provided by randomized treatment group.

Converters by Month 7 are subjects who have a negative culture at Month 7, and have achieved culture conversion by one of the following:

- MAC culture negative at Month 6 after adjustment for non-productive sputum, or
- Missing MAC culture at Month 6, and one of the below:
  - Achieved culture conversion (2 consecutive monthly negative sputum cultures), have negative culture after conversion, do not have recurrence after conversion, with at most 1 missing sputum assessment at or before Month 5, or
  - Negative culture at Month 5

Non-converters by Month 7 are subjects who satisfy one of the following criteria:

- Die after randomization, or
- Have a positive MAC culture at Month 6 and/or Month 7 (after adjustment for non-productive)

11.3.1. Analysis

Analysis of this endpoint will follow Section 9.3.1.2.

11.3.1.1. Data Handling

For the purpose of the analysis the influence of ICEs (Section 7.5) and the presence of the missing data on the estimation of culture conversion proportion by Month 7 will be taken into consideration.

Culture conversion by Month 7 will be handled by following rules:

1. Derive culture conversion by Month 7 using the rules above. Retrieved sputum assessments will be used in the analysis, ie, collected after early termination of ALIS/ELC (see Section 7.4 for definition)
2. Data for subjects who complete 6 months of the randomized treatment however conversion status by Month 7 is not available will be imputed based on the observed status distribution from the subjects who completed 6 months of randomized treatment (ALIS/ELC, AZI, and ETH), have Month 7 conversion status determined, and were randomized to the same treatment group. This approach is consistent with MAR approach imputation.
3. When retrieved assessments are unavailable or #1 does not provide conversion status by Month 7, the missing Month 7 conversion status will be imputed as follows:

- For subjects experiencing ICE (other than death), their missing Month 7 conversion status will be imputed based on the retrieved Month 7 conversion distribution from the subjects experiencing ICE (retrievers). MNAR imputation of the data for those subjects experiencing ICE is applied.
- For subjects not experiencing ICE, their missing Month 7 conversion status will be imputed based on the observed status distribution from the subjects who completed 6 months of randomized treatment, have Month 7 conversion status determined, and were randomized to the same treatment group. This approach is consistent with MAR approach imputation.

The ELC treatment group (including retriever) will be used instead if the ICE retriever subgroup is too small to allow imputations as described above. The decision as to which group will be used in the imputation will be determined prior to unblinding at the blinded data review meeting.

Imputation details are included in the Appendix I.

11.4. Correlations

Correlations between QOL-B (Respiratory Symptoms Domain), PROMIS F-SF 7a (raw score) (denoted 'PROs' below) and microbiology variables will be investigated. Missing data for this analysis will not be multiply imputed, however all other rules described in Sections 9.3.1.2 and 9.3.2.2 that allow deterministically assign missing values will be applied.

- Change from baseline to Month 6 in PROs vs Culture conversion by Month 6
- Change from baseline to Month 7 in PROs vs Culture conversion by Month 6

- Change from baseline to Month 6 in PROs vs Culture conversion by Month 7
- Change from baseline to Month 7 in PROs vs Culture conversion by Month 7

Correlations will be evaluated by treatment group and for overall using point biserial correlation and ANOVA/ANCOVA with response variable of change from baseline in PRO, and independent variables culture conversion status, and treatment (if appropriate). Basic statistics of change from baseline in PRO scores by converter status will also be provided.

In addition, plots of change from baseline PRO mean scores over time will be presented for converters and non-converters.

11.5. Intercurrent Event Assessment

The assessment of ICEs is descriptive and will be performed to investigate the occurrence in the clinical trial setting.

The frequency and percentage of subjects experiencing each of the ICE types will be tabulated by treatment group.

In addition, the time to intercurrent event will be illustrated with Kaplan-Meier plot. Discontinuation of ALIS/ELC due to non-ICE reasons are considered censored and set to the date of last dose of ALIS/ELC.

12. SAFETY

Unless otherwise stated all summaries will have corresponding listings.

The summaries will be according to the actual treatment received; any deviation from the treatment received will be listed.

12.1. Treatment and Study Duration

1) Duration of treatment will be summarized descriptively; separately for each study drug [ALIS/ELC, AZI, ETH] and for all study drugs combined.

   duration of treatment (days) = date of last dose – date of first dose + 1

This definition does not account for protocol-allowed interruptions.

2) Study drug exposure will be summarized descriptively; separately for each study drug [ALIS/ELC, AZI, ETH] and for all study drugs combined.

   duration of exposure (days) =
   date of last dose - date of first dose + 1 - total number of days with protocol-prescribed prescribe interruptions due to safety reasons

   For all study drugs combined the derivation is

   duration of exposure (days) =
   date of last day all study drugs are concurrently administered -
   date of first day all study drugs are concurrently administered + 1 -
   total number of days any study drug was interrupted due to safety reasons

3) The duration of study will be calculated as number of days between randomization and end of study and summarized descriptively.

   duration of study (days) = end of study date – date of randomization + 1

12.2. Compliance

Subjects will be required to bring all their used and unused study drug supplies to in-clinic study visits during the treatment period or, if the visit is being conducted virtually, have all used and unused study drug supplies available for accountability review.

Compliance will be categorized (>120%, 80-120%, <80%) and tabulated (number and percentage of subjects).

Compliance (%) = 100% × Number of units used / number of expected units

where the unit for all study drugs is 'mg'.

Number of units used will be derived using the data from the form "Drug Accountability".

The expected number of units is the sum of all expected daily units from the first dose of the respective study drug reported on form "Prior and Concomitant Medications" until the last dose of the study drug reported on form "End of Treatment".

Protocol-allowed dose interruptions due to safety reasons are reported on eCRF form "Prescribed Dose Interruptions"; consequently, for the purpose of compliance calculations the number of expected units during these interruptions is 0.

Protocol-allowed dose adjustments will be reported on the form "Prior and Concomitant Medications" and can be identified by the product code "INVESTIGATIONAL DRUG". The prescribed dose in the reported interval is the dose (mg) reported on the form. A dose adjustment is protocol-allowed if the "Reason for treatment" is "Adverse event". If the dose frequency is adjusted to a value different to 'once daily', then the daily dose must be derived.

ETH tablets are available in doses of 100 mg and 400 mg. Tablets are combined to match a daily dose of 15 mg/kg. The **expected per-protocol dose of ETH** is the first dose reported on the form "Prior and Concomitant Medication" dose for each subject is the dose reported at the date of first dose on form "Prior and Concomitant Medications".

Table 6: Expected Daily Doses of Study Drugs

Study Drug	Interval	Expected Per-protocol Dose (mg/day)
ALIS/ELC	Protocol-allowed dose interruption due to safety reason	0
	Protocol-allowed dose adjustment due to safety reasons	as reported in EDC form CM
	Other *	590
AZI	Protocol-allowed dose interruption due to safety reason	0
	Protocol-allowed dose adjustment due to safety reasons	as reported in EDC form CM
	Other *	250
ETH	Protocol-allowed dose interruption due to safety reason	0
	Protocol-allowed dose adjustment due to safety reasons	as reported in EDC form CM
	Other *	dose at the day of first ETH dose on EDC form CM

* 'Other' is every day between First Dose (from CM) and Last Dose (from EOT) which is not in the 2 above mentioned intervals (Protocol-allowed dose interruption due to safety reason, Protocol-allowed dose adjustment due to safety reasons)

12.3. Dose Interruption

Dose interruptions will be recorded in the subject's diary and eCRF. All dose interruptions reported are protocol-allowed interruptions due to safety reasons. Number and percent of subjects who interrupted study drug(s) will be presented.

Basic summaries of length of interruption (days) will be presented for each interruption. Dose interruption due to COVID-19 will be summarized and listed.

12.4. Adverse Events

The adverse event verbatim descriptions (Investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to primary SOC and PT using MedDRA.

Adverse events that occur between the time subject signs the ICF for the study and the time when subject receives his/her first dose of study drugs on Day 1 will be summarized as medical history and not as a TEAE unless the event meets the definition of an SAE.

TEAEs are those AEs that occurred on or after the date of first dose of study drugs and within 28 days after the last dose of ALIS/ELC, AZI, or ETH, whichever study drug is stopped last. The listing will indicate whether a non-TEAE occurred post-treatment with study drugs.

The following table describes rules to be applied in case of missing AE start date.

Table 7: TEAE Assignment in Case of Missing AE Start Date Elements

Missing elements of AE start	**Rule** (study drug start = first dose of **ALIS/ELC, AZI, or ETH, whichever is started first**)	**Classification**
Regardless of any missing information for AE start: AE end date < study drug start date		non-TEAE
Otherwise (ie, if AE end date ≥ study drug start date)		
day/month/year	all AEs	TEAE
day and month	AE start year ≥ study drug start year	TEAE
	AE start year < study drug start year	non-TEAE
day	AE start month/year ≥ study drug start month/year	TEAE
	AE start month/year < study drug start month/year	non-TEAE

The exposure-adjusted incidence rate (EAR) is defined as the number of subjects with a particular AE divided by the total time at risk for TEAEs among subjects in the respective study treatment group at risk of an initial occurrence of the event.

time at risk for TEAE (days) = minimum (date of last dose of study drug + 29, EOS date) – date of first dose of study drug,

where 'study drug' may be ALIS/ELC, AZI, and/or ETH.

The EAR will be presented for tables summarizing TEAE.

Duration of AEs will be calculated in days (see Section 7.6.1). If date of onset or end date of event is not complete, duration will be set to missing.

Tabulations that are displayed by SOC and PT will be ordered by descending order of total incidence of SOC and PT within each SOC. Tabulations of the following types will be presented:

- Overall incidence of TEAEs including the incidence of subjects with at least one:
  - TEAE
  - serious TEAE

  - severe TEAE
  - TEAE resulting in death
  - TEAE related to ALIS/ELC, related to AZI, related to ETH
  - serious TEAE related to ALIS/ELC, related to AZI, related to ETH
  - TEAESI
  - TEAE leading to ALIS/ELC withdrawal, AZI withdrawal, ETH withdrawal
  - TEAE related to COVID-19
- Subject incidence of TEAEs and total number of TEAEs by MedDRA SOC and PT:
  - TEAEs
  - TEAEs related to ALIS/ELC, related to AZI, related to ETH
  - serious TEAEs
  - serious TEAEs related to ALIS/ELC, related to AZI, related to ETH
  - TEAEs leading to ALIS/ELC withdrawal, AZI withdrawal, ETH withdrawal
  - TEAEs, PT with incidence of >5% in any treatment group
- Subject incidence of TEAEs by MedDRA SOC, PT, maximum severity. At each level of subject summarization, a subject will be classified at the highest reported severity. Missing severity will be classified as missing on the summary if there is no non-missing severity at the level of summarization.

All information pertaining to AEs noted during the study will be presented in a subject listing.

12.5. Treatment Emergent Adverse Events of Special Interest

The TEAESI category groups include the following:

- Allergic alveolitis
- Haemoptysis
- Bronchospasm *
- Exacerbation of underlying pulmonary disease *
- Ototoxicity
- Nephrotoxicity
- Neuromuscular disorders

* These TEAEs are additionally categorized by the Investigator. This judgment is listed but not summarized or used for identification of AESIs.

PTs for TEAESIs are listed as per Appendix H, and additional PTs may be added during the study conduct.

The incidence will be summarized by each TEAESI category and PT by study treatment group.

12.6. Deaths

A listing of all AEs resulting in death will be provided.

12.7. Rescue Therapy

Rescue therapy is defined as any change from the randomized treatment (ALIS + background regimen or ELC + background regimen) as prescribed in the study (includes drug, dose, frequency, route of administration) due to progression of MAC lung infection. Rescue therapy does not include changes from randomized treatment (eg, removal or replacement of drug) due to intolerance or AEs from study drugs.

It should be noted that rescue therapy does not mean initiating a more efficacious treatment. Treatment options for MAC lung disease known to be efficacious other than (at a minimum) the combination of a macrolide plus ethambutol already provided in the study are limited. Furthermore, these patients are failing initial course of therapy and should be considered refractory; recommended treatment in that case would be the addition of ALIS – which may or may not have already been provided as part of randomized treatment. Therefore, rescue therapy is specifically initiation of alternative treatment due to progression of MAC lung disease because current treatment has failed.

Subjects who receive rescue therapy will stop randomized treatment (ALIS + background regimen or ELC + background regimen), be treated by local standard of care or as recommended by the Investigator and will continue with their remaining scheduled study visits.

Data is collected on the appropriate eCRF pages.

A summary of number and percentage of subjects with rescue therapy will be provided.

12.8. Nebulizer Deficiency

ALIS/ELC is administered to subjects by oral inhalation using the [redacted] nebulizer system. TEAEs related to device deficiency will be summarized and listed.

12.9. Clinical Laboratory Evaluations

Numeric laboratory parameters (hematology, chemistry (incl CRP), and urinalysis) will be summarized using descriptive statistics at baseline and at each post-baseline timepoint for the safety analysis set. Changes from baseline will also be summarized. Descriptive statistics at baseline and change from baseline is limited to continuous data.

Shift tables (ie, low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to post-baseline visits. Reference ranges established by the central laboratory will be used to determine shifts.

Clinical laboratory results will be provided in subject listings for the safety analysis set. Subjects experiencing ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN according to Hy's Law will be listed.

A summary of counts of subjects with an abnormal laboratory value at any visit including unscheduled will also be provided.

12.10. Vital Signs

Systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, height, and weight will be collected at protocol-specified visits.

Descriptive summaries of actual values and changes from baseline will be based on available data and will be provided by visit.

12.11. Physical Examination

Any abnormalities observed at Screening will be recorded in the medical history or as AEs if they occur after randomization.

Dates of Physical Examinations will not be listed.

12.12. Audiology Tests

Audiology testing will be performed at the protocol-specified visits. Frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz will be evaluated for each ear using air conduction.

The actual, baseline, and change from baseline audiology test results will be summarized descriptively by visit, frequency, and ear.

In addition, the data will be summarized by subjects who meet CTCAE v5.0 grading criteria for hearing impairment included in Table 8:

Table 8: Hearing Impaired CTC Grade

Grade	Criteria
1	Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear.
2	Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear.
3	Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear
4	Decrease in hearing to profound bilateral loss (absolute threshold >80 dB hearing loss at 2 kHz and above)

The baseline hearing test is the threshold for deriving the grade. Subjects who do not meet any of the above CTC grades will not be summarized.

The audiology results will be tabulated (number and percentage of subjects) by CTC grade (1, 2, 3, 4) within treatment and total groups. When presenting results, the highest CTC grade at a post-baseline visit (including unscheduled visits) will be used. The denominator for frequency calculation is the safety analysis set.

12.13. Pregnancy test

Pregnancy test results will be listed.

12.14. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug dictionary.

Prior medications are those medications taken before the first dose of study drug. A medication that starts prior to first dose but continues after the first dose of study drug is classified both in prior and concomitant medications. A medication is classified as 'Prior' if the eCRF question 'Started prior to study treatment' is answered Yes.

Concomitant medications are those medications taken on or after the first dose of study drug, ie, the end date is on or after the date of the first dose of study drug(s) or ongoing. If the end date of a medication is partially missing, and the possible interval for the end date includes the date of the first study drug dose, the medication is considered 'Concomitant'.

Prior and concomitant medications will be summarized separately. The number and percentage of subjects reporting the medication will be presented for subjects using at least 1 medication, at least one medication at the Anatomical Therapeutic Class Level 4 (ATC4) level, and by preferred term within ATC4. If ATC Level 4 is not available, ATC Level 3 is used instead. If ATC Level 3 is not available, ATC Level 2 is used instead.

Non-pharmacological procedures will be listed but not summarized.

13. CHANGES TO PROTOCOL-SPECIFIED ANALYSIS

The following table summarizes changes to the protocol-specified analyses, since no further protocol amendments are planned prior to unblinding of the study and finalization of this SAP.

Table 9: Changes to Protocol-Specified Analyses

Revision	Protocol Section	SAP Section	Rationale
End of treatment	3.4: "The EOT is defined as the date when the EOT visit occurs."	4.2: "The end of treatment (EOT) is defined as the date of the last dose of ALIS/ELC, AZI and/or ETH whichever study drug dose is taken last."	The definition clarifies the possibility of different study drugs discontinuation dates.

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APPENDIX A. QOL-B

Blue figures: as coded in eCRF

QOL-B v3.1_(US)_lung condition – English 30 April 2021

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have lung conditions. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Quality of Life *Please check the box indicating your answer.*

During the past week, to what extent have you had difficulty:	A lot of difficulty	Moderate difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as gardening or exercising	☐ 1	☐ 2	☐ 3	☐ 4
2. Walking as fast as others (family, friends, etc.)	☐ 1	☐ 2	☐ 3	☐ 4
3. Carrying heavy things, such as books, groceries, or shopping bags	☐ 1	☐ 2	☐ 3	☐ 4
4. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3	☐ 4

During the past week, indicate how often:	Always	Often	Sometimes	Never
5. You felt well	☐ 4	☐ 3	☐ 2	☐ 1
6. You felt tired	☐ 1	☐ 2	☐ 3	☐ 4
7. You felt anxious	☐ 1	☐ 2	☐ 3	☐ 4
8. You felt energetic	☐ 4	☐ 3	☐ 2	☐ 1
9. You felt exhausted	☐ 1	☐ 2	☐ 3	☐ 4
10. You felt sad	☐ 1	☐ 2	☐ 3	☐ 4
11. You felt depressed	☐ 1	☐ 2	☐ 3	☐ 4

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QOL-B v3.1_(US)_lung condition – English 30 April 2021

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Are you currently on any treatments (such as oral or inhaled medications; PEP or Flutter® device, chest PT, or Vest) for your lung condition?

☐ Yes ☐ No (Go to Question 15 on the next page)

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for your lung condition make your daily life more difficult?
1. Not at all 4
2. A little 3
3. Moderately 2
4. A lot 1

13. How much time do you currently spend each day on your treatments for your lung condition?
1. A lot 1
2. A moderate amount 2
3. A little 3
4. Almost none 4

14. How difficult is it for you to fit in your treatments for your lung condition each day?
1. Not at all 4
2. A little 3
3. Moderately 2
4. Very 1

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?
1. Excellent 4
2. Good 3
3. Fair 2
4. Poor 1

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 QOL-B, Version 3.1_(US)_lung condition Page 2

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QOL-B v3.1_(US)_lung condition – English 30 April 2021

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Please select a box indicating your answer.

*Thinking about your health during the past **week**, indicate the extent to which each sentence is true for you.*

	Completely true	Mostly true	A little true	Not at all true	
16. I have to limit vigorous activities, such as walking or exercising	☐ 1	☐ 2	☐ 3	☐ 4	
17. I have to stay at home more than I want to	☐ 1	☐ 2	☐ 3	☐ 4	
18. I am worried about being exposed to others who are sick	☐ 1	☐ 2	☐ 3	☐ 4	Doesn't apply
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. I lead a normal life	☐ 4	☐ 3	☐ 2	☐ 1	
21. I am concerned that my health will get worse	☐ 1	☐ 2	☐ 3	☐ 4	
22. I think my coughing bothers others	☐ 1	☐ 2	☐ 3	☐ 4	
23. I often feel lonely	☐ 1	☐ 2	☐ 3	☐ 4	
24. I feel healthy	☐ 4	☐ 3	☐ 2	☐ 1	
25. It is difficult to make plans for the future (vacation, attending family events, etc.)	☐ 1	☐ 2	☐ 3	☐ 4	
26. I feel embarrassed when I am coughing	☐ 1	☐ 2	☐ 3	☐ 4	

Please circle the number or check the box indicating your answer.

*During the **past week**:*

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?
    1. You have had no trouble keeping up 4
    2. You have managed to keep up but it has been difficult 3
    3. You have been behind 2
    4. You have not been able to do these activities at all 1

	Always	Often	Sometimes	Never
28. How often does having your lung condition get in the way of meeting your work, household, family, or personal goals?	☐ 1	☐ 2	☐ 3	☐ 4

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QOL-B v3.1_(US)_lung condition – English 30 April 2021

QOL-B QUALITY OF LIFE QUESTIONNAIRE

Section II. Respiratory Symptoms *Please check the box indicating your answer.*

Indicate how you have been feeling during the past week:	A lot	A moderate amount	A little	Not at all
29. Have you felt congestion in your chest?	☐ 1	☐ 2	☐ 3	☐ 4
30. Have you been coughing during the day?	☐ 1	☐ 2	☐ 3	☐ 4
31. Have you had to cough up mucus?	☐ 1	☐ 2	☐ 3	☐ 4

32. Has your sputum been mostly:
4 ☐ Clear 3 ☐ Clear to yellow 2 ☐ Yellowish-green
1 ☐ Brownish-dark 00 ☐ Green with traces of blood 0 ☐ Don't know

How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath with greater activity, such as housework or yardwork?	☐ 1	☐ 2	☐ 3	☐ 4
34. Have you had wheezing?	☐ 1	☐ 2	☐ 3	☐ 4
35. Have you had chest pain?	☐ 1	☐ 2	☐ 3	☐ 4
36. Have you had shortness of breath when talking?	☐ 1	☐ 2	☐ 3	☐ 4
37. Have you woken up during the night because you were coughing?	☐ 1	☐ 2	☐ 3	☐ 4

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

 QOL-B, Version 3.1_(US)_lung condition Page 4

APPENDIX B. PROMIS F-SF 7A

Blue figures: as coded in eCRF

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5 1	☐ 4 2	☐ 3 3	☐ 2 4	☐ 1 5

APPENDIX C. EXACT

Blue figures: as coded in eCRF

1. Did your chest feel congested today?		0. Not at all
		1. Slightly
		2. Moderately
		3. Severely
		4. Extremely
2. How often did you cough today?		0. Not at all
		1. Rarely
		2. Occasionally
		3. Frequently
		4. Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0	0. None at all
	1	**1. A little**
	01	**1. Some**
	2	2. A great deal
	3	3. A very great deal
		NOTE: Score "A little" and "Some" the same.
4. How difficult was it to bring up mucus (phlegm) today?		0. Not at all
		1. Slightly
		2. Moderately
		3. Quite a bit
		4. Extremely
5. Did you have chest discomfort today?		0. Not at all
		1. Slight
		2. Moderate
		3. Severe
		4. Extreme
6. Did your chest feel tight today?		0. Not at all
		1. Slightly
		2. Moderately
		3. Severely
		4. Extremely

Blue figures: as coded in eCRF

7. Were you breathless today?		0. Not at all
		1. Slightly
		2. Moderately
		3. Severely
		4. Extremely
8. Describe how breathless you were today:	0	0. Unaware of breathlessness
	1	1. Breathless during strenuous activity
	2	2. Breathless during light activity
	3	**3. Breathless when washing or dressing**
	03	**3. Present when resting**
		NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.
9. Were you short of breath today when performing your usual personal care activities like washing or dressing?	0	0. Not at all
	1	1. Slightly
	2	2. Moderately
	3	**3. Severely**
	03	**3. Extremely**
	4	4. Too breathless to do these
		NOTE: Score "Severely" and "Extremely" the same.
10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?	0	0. Not at all
	1	1. Slightly
	2	2. Moderately
	3	**3. Severely**
	03	**3. Extremely**
	003	**3. Too breathless to do these**
		NOTE: Score "Severely," "Extremely," and "Too breathless to do these" the same.
11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	0	0. Not at all
	1	1. Slightly
	2	2. Moderately
	3	**3. Severely**
	03	**3. Extremely**
	003	**3. Too breathless to do these**
		NOTE: Score "Severely," "Extremely", and "Too breathless to do these" the same.

Blue figures: as coded in eCRF

12. Were you tired or weak today?		0. Not at all
		1. Slightly
		2. Moderately
		3. Severely
		4. Extremely
13. Last night, was your sleep disturbed?		0. Not at all
		1. Slightly
		2. Moderately
		3. Severely
		4. Extremely
14. How scared or worried were you about your lung problems today?	0	0. Not at all
	1	1. Slightly
	2	2. Moderately
	3	**3. Severely**
	03	**3. Extremely**
		NOTE: Score "Severely" and "Extremely" the same.

APPENDIX D. SGRQ – WEIGHTS FOR QUESTIONS REQUIRING SINGLE RESPONSE

Column **Field** refers to the Field Name on the annotated eCRF.

Blue figures: as coded in eCRF

	Field	almost every day 1	several days a week 2	a few days a month 3	only with respiratory infections 4	not at all 5
Q1	SGRQ0202	80.6	63.2	29.3	28.1	0.0
Q2	SGRQ0203	76.8	60.0	34.0	30.2	0.0
Q3	SGRQ0204	87.2	71.4	43.7	35.7	0.0
Q4	SGRQ0205	86.2	71.0	45.6	36.4	0.0

		more than 3 times 1	3 times 2	2 times 3	1 time 4	none of the time 5
Q5	SGRQ0206	86.7	73.5	60.3	44.2	0.0

		a week or more 1	3 or more days 2	1 or 2 days 3	less than a day 4	if Q5 = 'none of the time'
Q6	SGRQ0207	89.7	73.5	58.8	41.9	0.0

		no good days 1	1 or 2 good days 2	3 or 4 good days 3	nearly every day was good 4	every day was good 5
Q7	SGRQ0208	93.3	76.6	61.5	15.4	0.0

		yes 1	no 2	Do you have a wheeze = no
Q8	SGRQ0209	62.0	0.0	0.0

		The most important problem I have 1	Causes me quite a lot of problems 2	Causes me a few problems 3	Causes no problems 4
Q9	SQRG0210	83.2	82.5	34.6	0.0

		My respiratory problems made me stop working altogether 1	My respiratory problems interfere with my job or made me change my job 2	My respiratory problems do not affect my job 3
Q10	SGQR0211	88.9	77.6	0.0

	CAVE: reversely coded	It stops me doing everything I would like to do 4	It stops me doing most of the things I would like to do 3	It stops me doing one or two things I would like to do 2	It does not stop me doing anything I would like to do 1
Q17	SGQR0251	96.7	84.2	42.0	0.0

APPENDIX E. SGRQ – WEIGHTS FOR QUESTIONS ALLOWING MULTIPLE RESPONSES

The following questions can be answered TRUE or FALSE. If the answer is TRUE, the item is considered with the respective weight in the component score. If the answer is FALSE, the weight is 0.

Column **Field** refers to the Field Name on the annotated eCRF.

Section 2, Question 11 These are questions about what activities usually make you feel short of breath these days.	**Field**	**Weight**
Sitting or lying still	SGRQ0212	90.6
Getting washed or dressed	SGRQ0213	82.8
Walking around the home	SGRQ0214	80.2
Walking outside on the level	SGRQ0215	81.4
Walking up a flight of stairs	SGRQ0216	76.1
Walking up hills	SGRQ0217	75.1
Playing sports or games	SGRQ0218	72.1

Section 3, Question 12 These are more questions about your cough and shortness of breath these days.	**Field**	**Weight**
My cough hurts	SGRQ0219	81.1
My cough makes me tired	SGRQ0220	79.1
I get breathless when I talk	SGRQ0221	84.5
I get breathless when I bend over	SGRQ0222	76.8
My cough or breathing disturbs my sleep	SGRQ0223	87.9
I get exhausted easily	SGRQ0224	84.0

Section 4, Question 13 These are questions about other effects that your respiratory problems may have on you these days.	**Field**	**Weight**
My cough or breathing is embarrassing in public	SGRQ0225	74.1
My chest trouble is a nuisance to my family, friends or neighbours	SGRQ0226	79.1
I get afraid or panic when I cannot get my breath	SGRQ0227	87.7
I feel that I am not in control of my chest problem	SGRQ0228	90.1
I do not expect my chest to get any better	SGRQ0229	82.3
I have become frail or an invalid because of my chest	SGRQ0230	89.9
Exercise is not safe for me	SGRQ0231	75.7
Everything seems too much of an effort	SGRQ0232	84.5

Section 5, Question 14 These are questions about your respiratory treatment.	**Field**	**Weight**
My medication does not help me very much	SGRQ0233	88.2
I get embarrassed using my medication in public	SGRQ0234	53.9
I have unpleasant side effects from my medication	SGRQ0235	81.1
My medication interferes with my life a lot	SGRQ0236	70.3

Section 6, Question 15 These are questions about how your activities might be affected by your respiratory problems.	**Field**	**Weight**
I take a long time to get washed or dressed	SGRQ0237	74.2
I cannot take a bath or shower, or I take a long time	SGRQ0238	81.0
I walk more slowly than other people, or I stop for rests	SGRQ0239	71.7
Jobs such as housework take a long time, or I have to stop for rests	SGRQ0240	70.6
If I walk up one flight of stairs, I have to go slowly or stop	SGRQ0241	71.6
If I hurry or walk fast, I have to stop or slow down	SGRQ0242	72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	SGRQ0243	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	SGRQ0244	71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	SGRQ0245	63.5

Section 7, Question 16 We would like to know how your respiratory problems usually affect your daily life.	**Field**	**Weight**
I cannot play sports or games	SGRQ0246	64.8
I cannot go out for entertainment or recreation	SGRQ0247	79.8
I cannot go out of the house to do the shopping	SGRQ0248	81.0
I cannot do housework	SGRQ0249	79.1
I cannot move far from my bed or chair	SGRQ0250	94.0

APPENDIX F. FACIT-FATIGUE SUBSCALE

			Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	reverse	0	1	2	3	4
HI12	I feel weak all over	reverse	0	1	2	3	4
An1	I feel listless ("washed out")	reverse	0	1	2	3	4
An2	I feel tired	reverse	0	1	2	3	4
An3	I have trouble starting things because I am tired	reverse	0	1	2	3	4
An4	I have trouble finishing things because I am tired	reverse	0	1	2	3	4
An5	I have energy		0	1	2	3	4
An7	I am able to do my usual activities		0	1	2	3	4
An8	I need to sleep during the day	reverse	0	1	2	3	4
An12	I am too tired to eat	reverse	0	1	2	3	4
An14	I need help doing my usual activities	reverse	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	reverse	0	1	2	3	4
An16	I have to limit my social activity because I am tired	reverse	0	1	2	3	4

APPENDIX G. PGI-S INSTRUMENT

Blue figures: as coded in eCRF

PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Instructions: The following questions ask about the severity of your lung condition over the past week.

Please choose only 1 answer for each question.

BREATHING

1. How severe were your breathing symptoms (e.g., congestion, cough, mucus, wheezing, shortness of breath, etc.) **over the past week**?

1 ☐ Not at all
2 ☐ Mildly
3 ☐ Moderately
4 ☐ Very
5 ☐ Extremely

FATIGUE

2. How severe was your fatigue **over the past week**?

1 ☐ Not at all
2 ☐ Mildly
3 ☐ Moderately
4 ☐ Very
5 ☐ Extremely

APPENDIX H. ADVERSE EVENTS OF SPECIAL INTEREST

PT wording can slightly change between MedDRA versions. Also, PTs might be demoted to Lowest Level Terms.

AESI Category	Preferred term (MedDRA 25.1)
Allergic alveolitis	Hypersensitivity pneumonitis
	Pneumonitis
	Interstitial lung disease
Haemoptysis	Haemoptysis
Bronchospasm	Asthma
	Bronchial hyperreactivity
	Bronchospasm
	Dyspnoea
	Dyspnoea exertional
	Prolonged expiration
	Throat tightness
	Wheezing
Exacerbation of underlying pulmonary disease	Chronic obstructive pulmonary disease
	Infective exacerbation of chronic obstructive airways disease
	Infective exacerbation of bronchiectasis
Ototoxicity	Deafness
	Deafness neurosensory
	Deafness unilateral
	Dizziness
	Hypoacusis
	Presyncope
	Tinnitus
	Vertigo
	Deafness bilateral
Nephrotoxicity	Nephropathy toxic
	Azotaemia
	Oliguria
	Albuminuria
	Acute kidney injury
	Anuria
	Renal impairment
Neuromuscular disorder	Muscular weakness

AESI Category	Preferred term (MedDRA 25.1)
	Balance disorder
	Neuropathy peripheral

APPENDIX I. Multiple Imputation and Analysis Details

PRO imputations

Multiple Imputation method will be applied to impute the missing PRO change from baseline domain to Month 7 using SAS software as follows. Note that individual questions will not be imputed, just the calculated derived change from baseline to Month 7 value.

Imputations for subjects who experienced ICE (other than death) and whose retrieved assessments at Month 7 are unavailable

For subjects experiencing ICEs other than death, their missing change from baseline to Month 7 PRO will be imputed based on the retrieved assessment distribution (flagged as Ref_MNAR) from those retrievers who experienced ICE and are exposed to an altered treatment regimen after their ICEs. This approach is consistent with MNAR approach.

The missing data will be multiply imputed using PROC MI in SAS. The Sponsor believes that multiple imputation method is appropriate to appropriately estimate the mean and variance of the treatment effect. Fifty replications are sufficient to reflect variability of the imputations. The variables used in the MI model (predictors) will be randomization stratum (history of MAC lung infection, initial or subsequent), PRO score at baseline, and randomized treatment group. [redacted]

Imputations for subjects not experiencing ICE and whose retrieved assessments at Month 7 are unavailable

For subjects not experiencing ICE, their missing Month 7 PRO change from baseline will be imputed based on the observed data distribution (flagged as Ref_MAR) of subjects who completed 6 months of randomized therapy, have Month 7 PRO data assessment available, and are randomized to the same treatment group. This approach is consistent with MAR approach.

The missing data will be multiply imputed using PROC MI in SAS. The Sponsor believes that multiple imputation method is appropriate to appropriately estimate the mean and variance of the treatment effect. Fifty replications are sufficient to reflect variability of the imputations. The variables used in the MI model (predictors) will be randomization stratum (history of MAC lung infection, initial or subsequent) and PRO score at baseline. [redacted]

Imputations for subjects completing randomized therapy and whose assessments at Month 7 are unavailable

Data for subjects who complete 6 months of the randomized treatment however Month 7 PRO assessment is not available will be imputed based on the observed distribution from the subjects who completed 6 months of randomized treatment, have Month 7 PRO assessment, and were randomized to the same treatment group. This approach is consistent with MAR approach imputation. The missing data will be multiply imputed using PROC MI in SAS a described above.

Analysis methods

[redacted]

The ANCOVA analysis as specified in Section 9.3.2.2 will be performed using each of the 50 full sets. The 50 sets of results will be then combined using Rubin's rule implemented via SAS PROC MIANALYZE with the specification of their effect estimates together with the corresponding standard errors, resulting in a single set of estimates and testing statistics for the treatment effect.

Culture conversion imputations

Imputations for subjects who experienced ICE (other than death) and whose retrieved Month 6 conversion status is unavailable.

For subjects experiencing ICEs other than death, their missing Month 6 conversion status will be imputed based on the retrieved assessment distribution (flagged as Ref_MNAR) from those retrievers who experienced ICE and are exposed to an altered treatment regimen after their ICEs. This approach is consistent with MNAR methodology.

The missing data will be multiply imputed using PROC MI in SAS. Fifty replications are sufficient to reflect variability of the imputations. Logistic regression will be used in the MI procedure with model factors including randomization stratum (history of MAC lung infection, initial or subsequent) and randomized treatment group.

[redacted]

Imputations for subjects whose Month 6 conversion status is unavailable and who discontinued ALIS/ELC early due to a non-ICE event:

For subjects not experiencing ICE, their missing Month 6 conversion status will be imputed based on the observed data distribution (flagged as Ref_MAR) from the subjects who completed 6 months of randomized therapy, have Month 6 conversion status available, and are randomized to the same treatment group. This approach is consistent with MAR approach.

The missing data will be multiply imputed using PROC MI in SAS. Fifty replications are sufficient to reflect variability of the imputations. Logistic regression

will be used in the MI procedure with model factor randomization stratum (history of MAC lung infection, initial or subsequent). [redacted]

Imputations for subjects completing randomized therapy and whose conversion status at Month 6 is unavailable

Data for subjects who complete 6 months of the randomized treatment however Month 6 conversion status is not available will be imputed based on the observed distribution from the subjects who completed 6 months of randomized treatment, have Month 6 conversion status available, and were randomized to the same treatment group. This approach is consistent with MAR approach imputation. The missing data will be multiply imputed using PROC MI in SAS a described above.

Analysis methods

Following each round of imputation, a full set of subject's conversion status at Month 6 will be created by combining the observed values and sets of imputed values under the MNAR and MAR assumptions. This process will result in a total of 50 full sets.

The analysis as specified in Section 9.3.1.2 will be performed using each of the 50 full sets. The 50 sets of results will be then combined using Rubin's rule implemented via SAS PROC MIANALYZE with the specification of their effect estimates together with the corresponding standard errors, resulting in a single set of estimates and testing statistics for the treatment effect.

Imputation of conversion status by Month 7

The multiple imputation of culture conversion status by Month 7 follows the same approach as the imputation of culture conversion by Month 6 described above. Model will additionally include culture conversion status by Month 6 (possibly imputed) as additional model factor.

Imputation of PRO and conversion data based on ELC reference group

In case that the retriever group will be too small to use, the reference group will be subjects from ELC group. Final determination will be made at the time of BDRM.

Specifically, NMAR imputation will be based on those subjects from ELC group who have Month 7 data (including retrievers and subjects experiencing ICE). Imputation model will include (history of MAC lung infection, initial or subsequent), additionally, imputation of PRO change from baseline to Month 7 will include baseline PRO in the MI model.

MAR imputation will be based on those subjects from ELC group who stayed in the study and have Month 7 data.

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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
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Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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