STATISTICAL ANALYSIS PLAN

EBO-301: A Phase 2/3, Randomized, Double-blind, Placebo-controlled, Multicenter, Prospective Study to Assess the Efficacy, Safety, and Pharmacokinetics of Orally Administered Epetraborole in Patients with Treatment-refractory *Mycobacterium avium* Complex Lung Disease (MACrO2)

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15 April 2025

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Protocol Number:	EBO-301
Protocol Version/Date:	Version 5.0/07 June 2023
Investigational Product:	Epetraborole tablets
Sponsor:	AN2 Therapeutics, Inc. 1800 El Camino Real, Suite D Menlo Park, CA 94027 United States
SAP Version/Date:	Version 3.0/15 April 2025

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
[redacted]	
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[redacted]	
[redacted]	
[redacted]	

VERSION HISTORY

Version	Version Date	Description
0.4	20 January 2022	Initial version submitted to FDA
1.0	08 September 2023	Final Version 1.0 corresponding to Protocol Version 5.0
2.0	22 July 2024	• Clarify baseline definition ePRO entries corresponding to the Day 1 visit. • Clarify determination of Micro-ITT Population and PP Population. • Change categories in summary of patient disposition. • Eliminate summary and listing of COVID-19 related PDs. • Change BMI category cutpoint from 25 to 18.5 kg/m^2. • Add moxifloxacin and multi-drug resistance categories to baseline pathogen susceptibility and/or resistance summaries. • Add instructions for summaries of prior and concomitant antibiotics to consolidate preferred terms after elimination of "salt" suffixes. • Exclude visits with unreturned bottles of study drug from compliance calculation. • Eliminate PP Population in descriptive summary tables for secondary efficacy endpoints. • Replace MMRM approach with ANCOVA model for summary of continuous PROs by visit for Phase 2 analysis (and include both ANCOVA and MMRM approaches for Phase 3 analysis), changing response to change from baseline and allowing for inclusion of baseline score. • Add alternative response threshold for QOL-B respiratory domain score based on a psychometric analysis of the pooled data across groups and visits. • Add logistic regression to summary of response rate for PROs by visit, allowing for inclusion of baseline score or severity category. • Change summary of microbiological reinfection and relapse to summary of recurrence, relapse, and reinfection, and provide full definitions and method of determination for each at each planned analysis. • Replace spaghetti plots with line plots of mean score (+/- SD) for continuous PROs. • Add amikacin IV and amikacin (liposomal, inhaled) resistant MAC phenotype to list of efficacy by subgroup analyses. • Change the exploratory endpoint Time (in days) to improvement in PRO-based clinical response to time to first sustained PRO clinical response, and expand/clarify definitions for meeting event criteria. • Change the exploratory endpoint Time (in months) to improvement in colony count category to time to first sustained improvement in colony count category, and expand/clarify definitions for meeting event criteria.

Version	Version Date	Description
		• Add a new summary and corresponding listing of hemoglobin decreases on therapy and recovery by LFU visit for the End of Study analyses of each phase. • Add boxplots of change from baseline in Hgb, MCV, MCHC and RBC. • Add wording to Appendix for QOL-B domain scoring to clarify scoring for item 32, aligning with source reference. • Additional minor editorial additions for clarity.
3.0	15 April 2025	• Update Introduction Section to provide current rationale for the new SAP version generated after unblinding of Phase 2 data, with updates limited to Phase 3 analyses only. • Add clarification to Study Overview Section to indicate that this text corresponds to Protocol Version 5.0 and remains unchanged. • Update Efficacy Analysis Section to indicate that only a single database lock and End of Study analysis will be performed for Phase 3, rather than separate locks and analyses corresponding to Month 6 and End of Study, as originally planned. • Revise hierarchical testing order of secondary endpoints in the US and outside the US for Phase 3 • Replace the Phase 3 primary efficacy endpoint (in the US) of $MACRrO_2$ clinical response at Month 6 with change from baseline to Month 6 in QOL-B respiratory domain score. • Introduce $MACrO_2$ total scaled score as a new secondary. efficacy endpoint evaluated in Phase 3, and include in all subsequent analyses where key continuous PRO scores are to be summarized. • Provide new estimand details including data handling instructions for intercurrent events for new primary efficacy endpoint of change from baseline to Month 6 in QOL-B respiratory domain score. • Include additional sensitivity analyses of the primary efficacy endpoint based on alternative data handling rules for intercurrent events. • Consolidate Phase 3 Month 6 and Phase 3 End of Study analysis sections into overall sections for Phase 3 Secondary and Exploratory analyses. • Add scatterplots of colony count category versus change from baseline in continuous PRO score, by treatment and visit (Month 3 and Month 6), to list of analyses to assess concordance between PRO changes with microbiological changes. • Add line plots of mean (+/- SD) change from baseline in score over time for all continuous PROs, and remove bar plots of individual and key $MACrO_2$ symptoms over time • Remove Phase 3 exploratory efficacy analysis using logistic regression models for relative effect of key subgroups of interest and corresponding forest plots.

Version	Version Date	Description
		• Update Phase 3 exploratory efficacy analysis related to primary efficacy endpoints. • In Phase 3 exploratory efficacy analysis, replace time to first negative sputum culture through Month 4 and time to decrease in colony count category with time to first sustained improvement in QOL-B respiratory domain score by a threshold of 11.1 points and time to first sustained improvement in $MACrO_2$ total scaled score by a threshold of 11.3 points. • Add details of updated Phase 3 analyses to Changes from Protocol-Specified Statistical Analyses Section. • Add new AESIs related to pneumonitis for Phase 3 subjects. • Add new Appendix with scoring instructions for MACrO2 total scaled score. • Additional minor editorial additions for clarity.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALIS	Amikacin liposome inhalation suspension
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
CFU	Colony-forming units
CGIC	Clinician Global Impression of Change
CGIS	Clinician Global Impression of Severity
C_{max}	Maximum plasma drug concentration
CrCl	Creatinine clearance
CT	Computed tomography
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CSR	Clinical study report
ECG	Electrocardiogram
EDC	Electronic data capture
EOT	End of Therapy
ITT	Intend-to-Treat
LFU	Late Follow-up
LLN	Lower limit of normal
MAC	*Mycobacterium avium* complex
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration required to inhibit growth of 50% of organisms
MIC_{90}	Minimum inhibitory concentration required to inhibit growth of 90% of organisms
NTM	Nontuberculous mycobacteria
OBR	Optimized background regimen
PAP	Psychometric Analysis Plan
PD	Pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PRO	Patient-Reported Outcome
PT	Preferred term
QD	Once daily
QOL-B	Quality of Life-Bronchiectasis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGRQ-C	St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease patients
SOC	System organ class
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
Vd	Volume of distribution
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a description of the statistical methods to be implemented for the analysis of data from Study EBO-301 (Protocol Version 5.0, dated 07 June 2023), entitled "A Phase 2/3, Randomized, Double-Blind, Placebo-controlled, Multicenter, Prospective Study to Assess the Efficacy, Safety, and Pharmacokinetics of Orally Administered Epetraborole in Patients with Treatment-refractory *Mycobacterium avium* Complex Lung Disease ($MACrO_2$), " which was intended as a single study to support registration. EBO-301 was designed as a seamless trial randomizing patients to either treatment with epetraborole plus an optimized background regimen (OBR) or placebo plus an OBR, with no pause between Phase 2 and Phase 3 enrollment. Phase 2 enrollment was completed in September 2023 (n=80), at which time enrollment in the Phase 3 part of the trial started immediately.

On 08 August 2024, the Sponsor terminated the trial based on topline, unblinded results from the Phase 2 part of the study and notified the Agency accordingly. The Phase 2 study met its primary objective of demonstrating the ability to validate the $MACrO_2$ PRO and showed a preliminary efficacy signal favoring epetraborole based on a responder analysis (39.5% [15/38] epetraborole vs 25% [10/40] placebo, p=0.19). However, the epetraborole plus OBR arm was not superior to the placebo plus OBR arm in sputum culture conversion rate. Nonetheless, the Sponsor is continuing with an analysis of the Phase 3 study data because of the positive Phase 2 clinical efficacy data noted.

This SAP supports the planned analyses of the primary, secondary, and exploratory efficacy and safety endpoints identified for evaluation both in the United States (US) by the Food and Drug Administration (FDA) as well as for other regulatory agencies outside the US. In accordance with the above protocol, any primary or secondary objectives or endpoints and hierarchical testing procedures that differ between regions will be specifically designated by "in the US" for FDA regulatory interpretation or "outside the US" for other regulatory agency interpretation in this document.

As described in Section 2.2, this is a Phase 2/3 study with independently enrolled populations in Phase 2 and Phase 3, which were enrolled sequentially. Formal unblinded analyses were to be conducted after all patients in Phase 2 completed the Month 6 assessments, as well as at the end of the study. The analyses of the Phase 2 data were to be used to inform potential sample size re-estimation and potential modifications to the primary and secondary endpoints in Phase 3, which were to be reflected in a subsequent protocol amendment as applicable.

Version 2.0 of this SAP was finalized on 22 July 2024, prior to database lock and unblinding of the data through Month 6 of the Phase 2 part of the study. Modifications indicated in all subsequent versions of the SAP are limited to planned analyses of the independent Phase 3 part of the study, and supersede all planned analyses indicated in the final version of the protocol (Version 5.0, dated 07 June 2023). Any deviations from the SAP Version 2.0 or later after the database lock and analysis of Phase 2 data through Month 6 will be documented in the clinical study report (CSR). Any deviations from the current version of the SAP after the date of formal unblinding of all Phase 3 data will be documented in either a post hoc addendum to the SAP or the CSR, or both, and will be specifically noted as such in the CSR.

2 STUDY OVERVIEW

Study overview details below including study objectives, design, and endpoints correspond to those stated in Version 5.0 of the protocol (07 June 2023). Specific analyses proposed in this plan are detailed beginning in Section 3 (Statistical Methodology), and deviations from the analyses proposed in Version 5.0 of the protocol are itemized in Section 5 (Changes from Protocol-Specified Statistical Analyses).

2.1 Study Objectives

Phase 2 Part of the Study:

Primary Objectives in Phase 2

- *[In the US:]* To assess the measurement properties of the novel $MACrO_2$ Patient-Reported Outcome (PRO) instrument and to provide validation evidence in treatment-refractory *Mycobacterium avium* complex (MAC) lung disease, including the determination of symptom-based clinical response of epetraborole added to an optimized background regimen (OBR) (epetraborole + OBR) compared to placebo added to an OBR (placebo + OBR) using the $MACrO_2$ PRO
- *[Outside the US:]* To assess the microbiological response to oral epetraborole compared to placebo
- To assess the safety of oral epetraborole compared to placebo

Secondary Objectives in Phase 2

- *[In the US:]* To assess the microbiological response to oral epetraborole compared to placebo
- *[Outside the US:]* To assess the measurement properties of the novel $MACrO_2$ PRO instrument and to provide validation evidence in treatment-refractory MAC lung disease, including the determination of symptom-based clinical response of epetraborole added to an OBR (epetraborole + OBR) compared to placebo added to an OBR (placebo + OBR) using the $MACrO_2$ PRO
- To assess other PRO instruments (eg, Quality of Life-Bronchiectasis [QOL-B], nontuberculous mycobacteria [NTM] Symptoms Module, St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease patients [SGRQ-C]) in determining symptom/function-based clinical response to oral epetraborole compared to placebo
- To assess concordance between PRO symptom/function-based clinical response and microbiological response
- To assess microbiological reinfection and relapse
- To evaluate the plasma pharmacokinetics (PK) of oral epetraborole, including an interim PK analysis to assess exposures from approximately the first 16 epetraborole-treated patients

Exploratory Objectives in Phase 2

- To assess clinical and microbiological responses in subgroups (eg, age, amikacin liposome inhalation suspension [ALIS] use at baseline [pre-randomization], presence/absence of any fibrocavitary disease, MAC resistance phenotype)
- To assess pulmonary radiological response
- To assess microbiological response by epetraborole minimum inhibitory concentration (MIC)
- To evaluate postbaseline MAC isolates for decreased susceptibility to epetraborole compared to baseline
- To assess time to $MACrO_2$ PRO symptom-based clinical response
- To assess time to microbiological response
- To evaluate the proposed symptom-based clinical response definition that uses the $MACrO_2$ PRO, to understand patient perspectives on meaningful change more generally, through qualitative embedded interviews

Phase 3 Part of the Study:

Primary Objective in Phase 3

- *[In the US:]* To determine if epetraborole + OBR is superior to placebo + OBR in symptom-based clinical response as measured by the $MACrO_2$ PRO (the use of this PRO instrument in Phase 3 will be confirmed after Phase 2 analysis)
- *[Outside the US:]* To determine if epetraborole + OBR is superior to placebo + OBR in microbiological response

Secondary Objectives in Phase 3

- *[In the US:]* To determine if epetraborole + OBR is superior to placebo + OBR in microbiological response (key secondary objective)
- *[Outside the US:]* To determine if epetraborole + OBR is superior to placebo + OBR in symptom-based clinical response as measured by the $MACrO_2$ PRO (the use of this PRO instrument in Phase 3 will be confirmed after Phase 2 analysis) (key secondary objective)
- To assess concordance between PRO symptom/function-based clinical response and microbiological response
- To assess microbiological reinfection and relapse
- To assess the safety of oral epetraborole compared to placebo
- To assess the plasma PK of oral epetraborole

Exploratory Objectives in Phase 3

- To assess clinical and microbiological responses in subgroups (eg, age, ALIS use at baseline, presence/absence of any fibrocavitary disease, MAC resistance phenotype)
- To assess pulmonary radiological response
- To assess microbiological response by epetraborole MIC
- To evaluate postbaseline MAC isolates for decreased susceptibility to epetraborole compared to baseline
- To assess time to $MACrO_2$ PRO symptom-based clinical response
- To assess time to microbiological response

2.2 Study Design

2.2.1 Overview

Refer to Protocol Section 3.1 Summary of Study Design for full details of the study overview.

Briefly, this is a pivotal Phase 2/3, double-blind, placebo-controlled study of epetraborole + OBR versus placebo + OBR in patients with treatment-refractory MAC lung disease. This study will enroll adult patients with treatment-refractory MAC lung disease who meet all eligibility criteria.

This study features a sequential Phase 2/3 approach with an initial Phase 2 assessment of clinical responses (based on clinical symptoms and/or functional assessments), microbiological responses, safety, and PK associated with oral epetraborole, prior to the superiority analysis of oral epetraborole versus placebo in the Phase 3 part of the study.

In both the Phase 2 and Phase 3 parts of the study, each patient will complete multiple PRO measures including $MACrO_2$, QOL-B, NTM Symptoms Module, SGRQ-C, and global patient and clinician assessment scales (Patient Global Impression of Severity [PGIS], Patient Global Impression of Change [PGIC], Clinician Global Impression of Severity [CGIS], Clinician Global Impression of Change [CGIC]), and Meaningful Change Question (to be answered after each completion of the PGIC). An electronic PRO system will be used during the study to allow patients to complete the study questionnaires electronically.

The $MACrO_2$ PRO will be completed twice before the first dose of study drug to assess test-retest reliability (within 1 to 2 weeks prior to randomization, and on randomization day prior to study drug administration) and once weekly for the first 6 months of the study; other PROs and global assessment scales will be completed at baseline and once monthly for the first 6 months of the study. The QOL-B, NTM Symptoms Module, SGRQ-C, and PGIS will also be completed during Screening for test-retest reliability assessment. The PGIC, CGIC, and Meaningful Change Question will not be completed at baseline. After Month 6, all PROs will be completed every 3 months (84 days ±7days), at End of Therapy (EOT), and at Late Follow Up (LFU). Sputum samples for microbiological assessments will be collected during the Screening period, once monthly for the first 6 months of the study, and then every 3 months (84 days ±7days), at EOT, and at LFU.

Results from the Phase 2 part of the study ongoing will inform the specific PRO and the clinical response definition selected to measure the primary endpoint, and the sample size re-estimations to be used, in the Phase 3 part of the study.

2.2.2 Number of Patients

A total of approximately 314 patients will be enrolled in this Phase 2/3 study:

- The Phase 2 part of the study will consist of approximately 80 patients randomized in a 1:1 ratio (40 patients in the epetraborole + OBR group and 40 patients in the placebo + OBR group). Randomization will be stratified by baseline use of ALIS and age at informed consent (<65 years versus ≥65 years).
- The Phase 3 part of the study will consist of approximately 234 patients randomized in a 2:1 ratio (156 patients in the epetraborole + OBR group and 78 patients in the placebo + OBR group). Randomization will be stratified by baseline use of ALIS and the presence or absence of any fibrocavitary disease. The number of patients in the Phase 3 part of the study may be adjusted based on the results of Phase 2 analyses.

2.2.3 Study Duration

For the Phase 2 and Phase 3 parts of the study, the duration of study participation for each patient, not including Screening, will be up to approximately 19 months (see additional details in Protocol Section 3.1.1). Study participation for each patient includes the following:

- **Screening Visit**: Within 8 weeks prior to randomization.
- **Treatment Period**: Day 1 to EOT; the treatment period for each patient will vary, up to a maximum of 16 months, depending on the patient's sputum culture results; see details in Protocol Section 3.1.1.
- **EOT Visit**: Within 7 calendar days after the last dose of study drug.
- **LFU Visit**: 3 months (84 days ±14 days) after the last dose of study drug.

2.2.4 Sites

This Phase 2/3 study will be conducted globally at approximately 140 sites.

2.2.5 Study Drug

- Epetraborole oral tablets: 250 mg
- Epetraborole dosage: 500 mg (two 250-mg oral tablets) once daily (QD)
- Placebo oral tablets: Matched to epetraborole tablets

- Placebo regimen: Matched to epetraborole dosage [two oral tablets once daily (QD)]

2.2.6 Analysis Timing

In the Phase 2 part of the study, prespecified members of the Sponsor and [redacted] biostatistics analysis teams will be unblinded to treatment assignment for data analyses after the last patient in Phase 2 completes all assessments for the Month 6 visit (including the Month 6+1 week PRO assessment); however, study staff conducting psychometric validation analyses will remain blinded. Patients, Investigators, and other study staff not directly associated with the statistical analysis will also remain blinded to treatment assignment through the last study visit (LFU) (see Study Blinding Plan).

Initial Phase 2 data analyses will include review of patient-reported outcome responses (including clinical symptom responses and functional assessments), microbiological, safety, and PK data collected at multiple time points through Month 6. All efficacy and psychometric endpoints conducted as part of the Phase 2 Month 6 analysis will be considered final at this time. Any efficacy endpoint data collected at any visits beyond Month 6 (e.g. EOT, LFU) will not be summarized at the time of this analysis.

The Phase 2 part of the study includes a blinded analyses to assess the psychometric properties (ie, reliability, validity, ability to detect change, and clinically meaningful within-patient changes in scores) of the "MACrO2 PRO" instrument. A Psychometric Analysis Plan (PAP) is included as a separate document. The Phase 2 psychometric data analyses will support selection and positioning of PRO measures as endpoints for Phase 3. Decisions will be based on the magnitude of item-level or domain-level (when appropriate) change, ability to detect change (responsiveness), and concordance with microbiological response data. The definition of clinical response to be used in the Phase 3 part of the study will be informed through the psychometric analyses conducted with the pooled blinded data from the Phase 2 part of the study. In addition, the Sponsor will review the unblinded clinical and microbiological outcomes from Phase 2 data through Month 6 to determine if the sample size for Phase 3 should be adjusted.

In the Phase 3 part of the study, prespecified members of the Sponsor and [redacted] biostatistics analysis teams will be unblinded to treatment assignment for data analyses after the last patient in Phase 3 completes all assessments for the Month 6 Visit; patients, Investigators, and other study staff not directly associated with the statistical analysis will remain blinded to treatment assignment through the last study visit (LFU) (see Study Blinding Plan). Initial Phase 3 data analyses will include a review of patient-reported clinical symptom responses, safety, PK, and microbiological data collected at multiple time points through Month 6. All efficacy endpoints conducted as part of the Month 6 analysis will be considered final at this time, and are expected to be used to support marketing applications with the FDA, PMDA, and additional regulatory agencies for approval of epetraborole for use in patients with treatment-refractory MAC lung disease. Any efficacy endpoint data collected at any visits beyond Month 6 (e.g. EOT, LFU) will not be summarized at the time of this analysis.

Final analyses of both phases through all planned study time points will be performed after all patients from each phase have completed treatment and all study visits, and the database for each phase has been fully locked. At such time, treatment assignments within each phase will be fully unblinded to all parties.

2.2.7 Sample Size Determination and Power

Phase 2: The Phase 2 sample size (n=80) is based on the planned psychometric evaluation of the $MACrO_2$ PRO and is a sample size which may indicate an initial efficacy signal from this part of the study. When evaluating the individual items of the $MACrO_2$ PRO (not a scale with a total score), analyses will be within-patient, and this blinded evaluation will include all patients from both treatment groups. As a result, sample size requirements are not as high as in studies evaluating measures with composite scores. Basing

assumptions on convergent correlations with 90% power, an alpha of 0.05, and expected R=0.4, the minimum sample size needed is 61; therefore, a total Phase 2 sample size of 80 patients will be appropriate (polychoric correlations will be assessed given the $MACrO_2$ PRO uses rating scales with five response options). In addition, using assumed true response rates of 30% for the epetraborole arm and 10% for the placebo arm for a PRO symptom-based clinical response (in the US) or a microbiological culture conversion response (outside the US), a Phase 2 evaluation in approximately 40 patients per arm would have 85% power to show a significant treatment effect using a 2-sided alpha of 0.2. Therefore, this sample size is considered sufficient to provide the potential to show a preliminary efficacy signal.

Phase 3: No data are available on symptom-based clinical response or minimal clinically important differences (MCIDs) using available PROs in patients with treatment-refractory MAC lung disease; therefore, previously published Month 6 sputum culture conversion rates in treatment-refractory MAC lung disease were used to initially estimate the number of patients expected to have an MCID improvement in PRO score, assuming a correlation between microbiological response and clinical symptom improvement. A Phase 3 study comparing ALIS + OBR versus OBR alone in patients with treatment-refractory MAC lung disease reported Month 6 sputum culture conversion rates of 29.0% compared with 8.9%, respectively, in the ITT population. Therefore, the initial sample size estimate for the Phase 3 part of the study assumes that the true number of patients experiencing an MCID improvement in PRO score is 30% for the epetraborole + OBR arm and 10% for the placebo + OBR arm. Assuming a 2:1 randomization and a 2-sided alpha of 0.05, a Phase 3 study of 186 patients with proven MAC lung disease (ie, in the Micro-ITT population) in the primary analysis (124 patients in the epetraborole + OBR arm and 62 patients in the placebo + OBR arm) would provide approximately 90% power, while also assuming when performing an analysis of proportions using the method of Miettinen and Nurminen. The total sample size for the Phase 3 part of the study is estimated to be 234 patients (156 patients in the epetraborole + OBR arm and 78 patients in the placebo + OBR arm) rather than 186 patients, to allow for approximately 20% of randomized patients to be excluded from the Micro-ITT Population due to lack of a study qualifying baseline culture (see Inclusion Criterion 3.a in Protocol Section 4.1); therefore, 186 patients are expected to be included in the Micro-ITT Population for the primary efficacy analysis. The sample size for Phase 3 will be reassessed after Phase 2 analyses, which will be based on data for all patients in Phase 2 through Month 6. Any needed sample size adjustment for Phase 3 will be determined by the Sponsor as part of the review of unblinded results from the fully independent Phase 2 data.

2.3 Study Endpoints

Phase 2 Part of the Study:

Primary Endpoints for Phase 2:

- *[In the US:]* Assessment of $MACrO_2$ PRO instrument psychometric properties (eg, reliability, validity, ability to detect change [responsiveness], and clinically meaningful within-patient changes in scores), including assessment of symptom-based clinical response between baseline and Month 3, and baseline and Month 6, defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms, in the Microbiological Intent-to-Treat (Micro-ITT) Population
- *[Outside the US:]* By-subject sputum culture conversion monthly through Month 6 in the Micro-ITT Population. Sputum culture conversion will be assessed using culture conversion based on 3 consecutive monthly negative sputum cultures for MAC
- Assessment of treatment-emergent adverse events (TEAEs) and changes from baseline in clinical laboratory values, electrocardiograms (ECGs), and vital sign changes in the Safety Population

Secondary Endpoints for Phase 2:

- *[In the US:]* By-subject sputum culture conversion monthly through Month 6 in the Micro-ITT Population. Sputum culture conversion will be assessed using culture conversion based on 3 consecutive monthly negative sputum cultures for MAC
- *[Outside the US:]* Assessment of $MACrO_2$ PRO instrument psychometric properties (eg, reliability, validity, ability to detect change [responsiveness], and clinically meaningful within-patient changes in scores), including assessment of symptom-based clinical response between baseline and Month 3, and baseline and Month 6, defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms, in the Micro-ITT Population
- By-subject microbiological improvement at Month 3 and Month 6 in the Micro-ITT Population. Microbiological improvement will be assessed using decrease in MAC colony counts of ≥1 category
- PRO symptom/function-based clinical response using mean changes in PRO domain scores (eg, QOL-B, NTM Symptoms Module, SGRQ-C), or improvement of ≥1 grade in the key symptom with no worsening of other symptoms in the $MACrO_2$ PRO, monthly through Month 6, in the Micro-ITT and Per-Protocol (PP) populations
- Concordance analysis of PRO symptom/function-based clinical response and microbiological response (by-patient sputum culture conversion and by-patient microbiological improvement) in the Micro-ITT Population
- Rates of reinfection (new pulmonary MAC infection caused by pathogen[s] different from the baseline MAC isolate) and relapse (pulmonary MAC infection caused by the same baseline MAC isolate) at Month 6, EOT, and LFU in the Micro-ITT Population
- Characterization of epetraborole plasma exposure in the population PK model

Exploratory Endpoints for Phase 2:

- Clinical response and microbiological response (by-subject sputum culture conversion and by-subject microbiological improvement) at Month 3 and Month 6 presented by age category, presence/absence of any fibrocavitary disease, ALIS use at baseline, and MAC resistance phenotype (ie, macrolide-resistant and amikacin-resistant) in the Micro-ITT Population
- Radiographic response at Month 6 and EOT, defined as overall change from baseline based on blinded central reading of chest computed tomography (CT) in the Micro-ITT Population
- By-subject microbiological response (by-subject sputum culture conversion and by-subject microbiological improvement) by epetraborole MIC at Month 6 in the Micro-ITT Population
- Rate of decreased susceptibility among postbaseline MAC isolates, defined as a ≥4-fold increase in epetraborole MIC relative to the baseline isolate MIC, among patients remaining MAC culture-positive at Month 4 or later in the Micro-ITT Population
- Time (in days) to improvement in PRO-based clinical response in the Micro-ITT Population
- Time (in months) to first negative sputum culture and decrease in MAC colony counts by ≥1 category in the Micro-ITT Population
- Qualitative assessment of the appropriateness of the proposed symptom-based clinical response definition that uses the $MACrO_2$ PRO in the Micro-ITT Population.

Phase 3 Part of the Study:

Primary Endpoint for Phase 3:

- *[In the US:]* Pending verification from the Phase 2 part of the study: $MACrO_2$ PRO symptom-based clinical response, defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms between baseline and Month 6 in the Micro-ITT Population

- *[Outside the US:]* By-subject sputum conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6 in the Micro-ITT Population

Secondary Endpoints for Phase 3:

- *[In the US:]* Key secondary endpoint: By-subject sputum conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6 in the Micro-ITT Population
- *[Outside the US:] Key secondary endpoint:* Pending verification from the Phase 2 part of the study: $MACrO_2$ PRO symptom-based clinical response, defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms between baseline and Month 6 in the Micro-ITT Population
- By-subject microbiological improvement at Month 3 and Month 6 using decrease in MAC colony counts of ≥1 category in the Micro-ITT Populations
- PRO symptom/function-based clinical response using mean changes in PRO domain scores (eg, QOL-B, NTM Symptoms Module, SGRQ-C), or improvement of ≥1 grade in the key symptom with no worsening of other symptoms in the $MACrO_2$ PRO, monthly through Month 6, in the Micro-ITT and Per-Protocol populations
- Concordance analysis of PRO symptom/function-based clinical response and microbiological response (by-subject sputum culture conversion and by-subject microbiological improvement) in the Micro-ITT Population
- Rates of reinfection (new pulmonary MAC infection caused by strain[s] different from the baseline MAC isolate) and relapse (pulmonary MAC infection caused by the same baseline MAC isolate) at Month 6, EOT, and LFU in the Micro-ITT Population
- Assessment of TEAEs and changes from baseline in clinical laboratory values, ECGs, and vital sign changes in the Safety Population
- Characterization of epetraborole plasma PK in the PK Population

Exploratory Endpoints for Phase 3:

- Clinical response and microbiological response (by-subject sputum culture conversion and by-subject microbiological improvement) at Month 3 and Month 6 presented by age category, presence/absence of any fibrocavitary disease, ALIS use at baseline, and MAC resistance phenotype (macrolide-resistant and amikacin-resistant) in the Micro-ITT Population
- Radiographic response at Month 6 and EOT, defined as overall change from baseline based on blinded central reading of chest CT in the Micro-ITT Population
- By-subject microbiological response (by-subject sputum culture conversion and by-subject microbiological improvement) by epetraborole MIC at Month 6 in the Micro-ITT Population
- Rate of decreased susceptibility among postbaseline MAC isolates, defined as a ≥4-fold increase in epetraborole MIC relative to the baseline isolate MIC, among patients remaining MAC culture-positive at Month 4 or later in the Micro-ITT Population
- Time (in days) to improvement in PRO-based clinical response in the Micro-ITT Population
- Time (in months) to first negative sputum culture and decrease in MAC colony counts by ≥1 category in the Micro-ITT Population

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Study days are calendar days, rather than 24-hour days. Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0. Any durations in days will be derived as event stop date – event start date + 1.

3.1.2 Definition of Baseline

For PRO data entered by the patient ($MACrO_2$, QOL-B, NTM Symptoms Module, SGRQ-C, or PGIS), baseline is defined as the last entry recorded by the patient on or prior to the first dose of study drug + 1 day (ePRO-specified close of window to further entry to patients).

For PRO data entered by the site (CGIS), baseline is defined as the last entry recorded by the patient on or prior to the first dose of study drug + 6 days (ePRO-specified close of window to further entry to sites).

For microbiological data, baseline pathogen(s) are determined based on MAC pathogens isolated from all MAC-positive respiratory samples collected within the 8-week Screening Period prior to the first dose of study drug, with specific representative baseline pathogen(s) confirmed by blinded Sponsor review.

For all other efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to first dose of study drug, including results from unscheduled visits if applicable.

3.1.3 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum. Summaries of continuous variables that have some values recorded using approximate values (e.g., "<" or ">" for safety laboratory results) will use the numeric part of the value in calculations, while listings will present the data in its original format (e.g. "<X.X").

3.1.4 Handling of Dropouts and Missing Data

Every effort will be made to collect all data at specified times. Missing data will be handled as outlined below:

- All missing and partial dates for AEs after randomization will be queried for a value. If no value can be obtained, substitutions will be made as follows:
  For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless 1) the first day of the month is before the date of administration of study drug and the month and year are the same as the month and year of the date of administration of study drug, and 2) the end date is on or after the date of administration of study drug or the end date is completely missing, in which case the start day will be set to the day of administration of study drug.
  For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless 1) January 1st is before the date of administration of study drug and the year is the same as the year of the date of administration of study drug, and 2) the end date is on or after the date of administration of study drug or the end date is completely missing, in which case the start day and month will be set to that of the date of administration of study drug.

For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the patient, in which case the end day will be set to that of the patient's last contact date.
For a missing end day and month where the year is present, the end day and month will be set to the patient's last contact date, unless the year of the patient's last contact date is greater than the end year, in which case the end day and month will be set to December 31st.
These substitutions will be used in analyses; however, the actual partial or missing date recorded on the eCRF will be presented in listings.

- Missing dates for prior and concomitant medications will be queried for a value. If no value can be obtained, missing data will be handled as follows:
  For a missing start date, 1) if only the day component is missing, the start day will be set to the first day of the month, and 2) if both day and month components are missing, the start day will be set to January 1st.
  For a missing end date, 1) if only the day component is missing, the end day will be set to the last day of the month, and 2) if both day and month components are missing, the end date will be set to December 31st.
- If no value can be obtained for times for events and assessments occurring after randomization, the time will not be imputed but will remain missing.
- Severity and causality assessments for adverse events cannot be missing. Missing data will be queried for a value.

For clinical and microbiological responses, missing data will be handled as follows:

- Missing symptom data from $MACrO_2$ PRO responses:
  - All $MACrO_2$ PRO responses with missing entries will trigger alerts and will be followed up for a complete response. However, if any remain only partially completed, the patient will be considered to have missing data if an assessment of any of their seven MAC lung disease symptom(s) are not made in the $MACrO_2$ PRO at the protocol-defined time points of Month 3 and Month 6. Patients with any missing or incomplete Month 3 or Month 6 $MACrO_2$ PRO symptom data will be defined as an indeterminate response at the corresponding time point (Month 3 or Month 6), and will be considered clinical non-responders for PRO symptom-based clinical response analyses in the Micro-ITT Population in both the Phase 2 and Phase 3 parts of the study. For model-based (MMRM) analyses of $MACrO_2$ PRO response over time, patients with one or more missing visits will be retained in the model, with no imputation methods applied to those missing results.
- Missing data from other PRO responses (QOL-B, NTM Symptoms Module, SGRQ-C, and the MACrO2 total scaled score analyzed in Phase 3):
  - If individual items within the PRO score are missing, the approved algorithm (See Appendix) for calculating the domain score or total score will scale the response to account for the missing items. However, if the number of missing items is more than the allowance of the algorithm to enable the scaling to be reliably performed, the score will be considered missing for that visit, and handled as an entirely missing visit as per the bullet above.
  - For analyses of domain scores or total scores, a longitudinal analysis will be performed which will include data recorded at all time points up to Month 6 and will provide estimates of treatment effect at the relevant time points (Months 3 and 6). Missing data is not expected, but if there is a larger than expected amount of missing data, further analyses to assess the impact of missing data may be undertaken using missing data imputation methods.

  - For analyses of QOL-B response, NTM Symptoms Module response, and SGRQ-C response, a patient will be considered to have missing data if the relevant score is not completed at the protocol-defined time points of Month 3 and Month 6. Patients with missing Month 3 or Month 6 data will be defined as an indeterminate response at the corresponding time point (Month 3 or Month 6), and will be considered clinical non-responders. For model-based analyses of PRO measures over time, patients with one or more missing visits will be retained in the model, with no imputation methods applied to those missing results.
- Missing microbiological culture data:
  - For patients with no available sputum for culture despite attempted sputum collection — and if the patient was previously sputum culture negative for MAC at their last post-baseline available monthly assessment — the microbiological outcome will be assessed as culture negative for that visit and the MAC colony count category will be assessed as "No growth on agar or broth" at that visit. All other patients with missing sputum culture results that impacted the ability to assess sputum culture conversion (i.e., 3 consecutive months of negative sputum cultures) or categorical decreases in MAC colony counts will be considered microbiological non-responders.
- Missing colony count data:
  - As it is not uncommon for MAC pathogens to grow on liquid culture media (broth) but not on agar media, it is anticipated that there will be some sputum samples for which colony count cannot be obtained. For each sputum specimen in which growth of a MAC pathogen is identified in broth but colony counts on agar are not available, such results will be assessed as missing. In cases where a baseline colony count is not available, such patients will be excluded from the denominator for all analyses of microbiological improvement. In cases of post-baseline visits where a MAC pathogen is grown in broth but a colony count is not available, such patients will be categorized as "Missing" in summary statistics and considered non-responders with regard to microbiological improvement at that visit. In cases of post-baseline visits where no growth is seen in broth and a colony count is not available, such patients will be categorized as "No growth on agar or broth" and colony count of 0 at that visit.

Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations. Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only patients with available data will be included in the denominators).

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population is defined as all patients who were randomized, regardless of whether they received any study drug.

3.2.2 Safety Population

The Safety Population is defined as all randomized patients who receive any amount of study drug. All safety data will be analyzed using the Safety Population. In the event that a patient is administered incorrect study drug (e.g., not administered the study drug assigned at randomization), the actual treatment received will be used for safety analyses. For patients who intermittently receive incorrect study drug, they will be included in the epetraborole group if they receive any epetraborole.

3.2.3 Micro-ITT Population

The Micro-ITT Population is defined as all patients who meet the definition for the ITT Population and have MAC culture-positive Pre-Study and Screening respiratory specimens (per Inclusion Criterion 3a). Primary endpoint analyses in both Phase 2 and Phase 3 parts of the study will be performed in this patient population. A Sponsor internal Data Review Committee (DRC) will review deviations of this inclusion criterion to make a final determination of the Micro-ITT Population according to details outlined in a separate Evaluability Review Plan.

3.2.4 Per-Protocol (PP) Population

The PP Population is defined as all patients in the ITT Population who completed the study with no important protocol deviations that may impact the primary efficacy assessment. Separate protocol deviation reviews will assess each deviation as important or non-important and, if important, whether they impact the primary efficacy endpoint, prior to each formal database lock and analysis. The PP Population will be a secondary population for analysis of the primary efficacy endpoint and key secondary endpoints.

The Sponsor DRC will review study data and important protocol deviations for determination of patient inclusion in the PP Population according to criteria outlined in a separate Evaluability Review Plan. Formal DRC data reviews will occur on a regular basis throughout the study. DRC members and decisions taken during the meetings will be documented in minutes and/or as comments in a PP review spreadsheet. The DRC members will be blinded to treatment assignment for all data reviews. Immediately prior to database lock and unblinding of each formal analysis as described in Section 2.2.6 (Analysis Timing), the final approved spreadsheet and SAS dataset are created using treatment-specific variables. Inclusion in the PP Population will be considered locked at database unblinding and may only be changed programmatically. Any instances of receipt of incorrect study drug will be determined programmatically after database lock and unblinding.

3.2.5 Pharmacokinetics (PK) Population

The PK Population is defined as all patients treated with at least 1 dose of epetraborole and at least 1 analyzable PK sample.

3.2.6 Full Analysis Set-PRO (FAS-PRO) (applicable to Phase 2 part only)

The psychometric analyses will be conducted using blinded data from the FAS-PRO, and all available data will be included. The Full Analysis Set is identical to the ITT Population. The FAS-PRO will include all randomized patients who have $MACrO_2$ PRO data at Screening and Day 1 (for test-retest reliability assessment), and at Day 1 and at least Month 3 and/or Month 6 (for all other calculations).

3.2.7 Embedded Interview Population (applicable to Phase 2 Part only)

Up to 40 Phase 2 patients who meet Micro-ITT Population and interview eligibility criteria (see protocol Section 7.5.6).

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened (signed informed consent), screened but not randomized (screen failures), and randomized will be summarized in total based on all screened patients. Patients with screen failure dates prior to the date of first randomization in Phase 3 will be considered screen failures in the Phase 2 part of the study, while those afterwards will be considered screen failures in the Phase 3 part of the study. As rescreening of previous screen failures was allowed per protocol, patients will

be counted in Phase 2 or Phase 3 summaries based on their date of randomization or last screen failure only. Reasons for premature discontinuation of study drug and withdrawal from the study will also be summarized. In the Month 6 analysis of Phase 2, counts and percentages of patients continuing study drug beyond Month 6, discontinuing study drug at Month 6, or prematurely discontinuing study drug prior to Month 6 will be presented, with reasons for discontinuation summarized separately for each category.

The number and percentage of patients in each analysis population together with reasons for exclusion from each population will be provided. A listing of all patients in the ITT Population will present their inclusion or exclusion and any reasons for exclusion from the Safety, Micro-ITT, and PP populations.

In addition, the following patient disposition categories will be summarized for the ITT Population and Micro-ITT Population by treatment in total:

- Patients who received study drug;
- Patients who did not receive study drug;
- Study drug completion status at the Month 6 analysis (Phase 2 only):
    - Patients who continued study drug beyond Month 6;
    - Patients who discontinued study drug at Month 6 (and reason);
    - Patients who prematurely discontinued study drug prior to Month 6 (and reason);
- Study drug completion status at the End of Study analysis:
    - Patients who completed the study drug;
    - Patients with premature discontinuation of study drug (and reason);
- Patients with premature discontinuation of study drug due to impacts of the COVID-19 pandemic;
- Patients who completed the study (only at the end of study analysis);
- Patients withdrawn from the study (and reason, only at the end of study analysis); and
- Patients withdrawn from the study due to impacts of the COVID-19 pandemic (only at the end of study analysis).

3.3.2 Protocol Deviations

Protocol deviations will be collected externally from the clinical database and categorized in accordance with a separate Protocol Deviation Plan, and will be tabulated in the ITT Population by treatment arm. The summary will include number and percentage of patients with ≥1 important protocol deviation (defined as CSR reportable deviation), ≥1 non-important protocol deviation (defined as CSR non-reportable deviation), and ≥1 important protocol deviation (CSR reportable deviation) of each category.

A listing of all protocol deviations, along with their categorization as important or non-important (CSR reportable or non-reportable), will be provided for all patients in the ITT Population.

3.3.3 Demographic and Baseline Characteristics

All tables in this section will be run for the ITT, Safety and Micro-ITT Populations. If the ITT and Safety Populations are confirmed to be identical for a given Phase, only results in the Safety Population will be presented.

Baseline demographics will be summarized by treatment group and overall to include age and age category at time of informed consent in years as recorded on the eCRF (<65 vs ≥65 years, as well as ≥18 to <65 years, ≥65 to <75, ≥75 years), sex, race (American Indian or Alaska Native/Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White/Other), ethnicity (Hispanic or Latino/Not Hispanic or Latino/ Not Reported), region (if enrolled in the US vs. outside the US (APAC), as well as by country), and BMI at screening and baseline (kg/m^2), as well as baseline BMI category (<18.5 vs ≥18.5 kg/m^2).

Baseline clinical characteristics will be summarized by treatment group and overall to include baseline underlying lung disease (bronchiectasis, presence/absence of any fibrocavitary disease, chronic obstructive pulmonary disease [COPD], other); baseline use of ALIS, estimated creatinine clearance (CrCl) based on central laboratory values (or if missing, EDC (electronic data capture) calculated local laboratory values) as calculated by Cockcroft Gault method (Cockcroft 1976) (<30, ≥30 to <60, ≥60 to <90, and ≥90 mL/min), time since initial MAC diagnosis (years) and time since first diagnosis of treatment refractory disease (years).

Results from Screening radiographic assessments as reported by the site investigator will be summarized by treatment arm and overall for all patients in the ITT, Safety, and Micro-ITT populations, including indications of whether the chest CT scan was performed, presence of abnormalities consistent with MAC lung disease, presence of any fibrocavitary disease, and evidence of cavities. Predominant NTM disease classification (non-cavitary nodular bronchiectatic, cavitary nodular bronchiectatic, fibrocavitary, or other) will be summarized. For those patients where evidence of cavities was indicated, summary statistics for the maximum diameter of largest cavity will be provided, along with a categorical distribution of maximum diameter size (<1.0 cm, ≥1.0 to ≤3.0 cm, >3.0 to ≤5.0 cm, and >5.0 cm from the EDC).

An overview of baseline OBR will be presented for all patients in the ITT, Safety, and Micro-ITT populations, including the number of antimicrobial agents in the baseline OBR regimen (0, 1, 2, 3, 4+), patients initiating any OBR therapy during Screening, antibiotic classes indicated in baseline OBR regimens (macrolide, ethambutol, rifamycin, inhaled liposomal amikacin [ALIS], non-liposomal amikacin, clofazimine, or other), and all unique combinations of antibiotic classes reported among baseline OBR regimens. Antibiotics will be included in the baseline OBR regimens if they are indicated as antimycobaterial agents administered for MAC lung disease and are reported as ongoing on the day of first dose of study drug. Patients will be counted as initiating any OBR therapy during Screening if one or more of their OBR therapies indicate a start date occurring between their earliest Screening date and the day prior to their first dose of study drug. Antibiotic classes will be determined based on WHO Drug Dictionary preferred term and/or drug name (see Section 3.3.6). All antibiotics included in the OBR regimen not counted in one of the pre-specified classes will be classified in the Other class. Patients will be counted at most once per antibiotic class.

Signs and symptoms (term and severity) will be summarized for baseline visit by treatment arm and overall for all patients in the ITT, Safety, and Micro-ITT populations, according to patient-reported entries in the $MACrO_2$ PRO. A frequency distribution of the key symptom selected at baseline will also be included.

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment and in total for each of the ITT, Safety, and Micro-ITT populations. Listings will be provided for all demographic and baseline variables for the ITT Population.

3.3.4 Baseline Pathogens

All summaries specified in this section will be presented in the Micro-ITT Population.

All MAC pathogens isolated from baseline sputum cultures will be summarized by treatment group and overall for patients in the Micro-ITT Population. Baseline pathogen summaries will be presented by genus and species.

All MAC pathogens isolated from sputum cultures will undergo identification at the regional or central microbiology laboratory and susceptibility testing at the central microbiology laboratory. Identification and susceptibility results from the central laboratory will be used by default for evaluability and response assessments where available; however, where central laboratory data are not available, local/regional laboratory data may be utilized if available. If more than one sputum sample is culture positive for the same species of MAC, the identification of the representative baseline or post-baseline pathogen will be determined by periodic reviews by a Sponsor Pathogen Review Committee in a blinded fashion according to a separate Pathogen Review Plan.

In vitro testing results of baseline MAC pathogen susceptibility to epetraborole, amikacin, ciprofloxacin, clarithromycin, clofazimine, doxycycline, ethambutol, linezolid, minocycline, moxifloxacin, rifabutin, rifampin, streptomycin, and trimethoprim/sulfamethoxazole will be separately summarized for all MAC pathogens by treatment group and overall for the Micro-ITT Population. Any isolates with no MIC value obtained will be listed as "missing" and excluded from the denominators. MIC summaries for study drugs will include summary statistics including minimum and maximum values as well as minimum inhibitory concentration required to inhibit growth of 50% of organisms (MIC_{50}) and minimum inhibitory concentration required to inhibit growth of 90% of organisms (MIC_{90}) values.

MIC_{50} and MIC_{90} values will be derived programmatically: MIC values will be ordered from lowest to highest with a greater than sign taking the highest and a less than or equal to sign taking the lowest value (e.g., >8 is higher than 8 and ≤0.5 is less than or equal to 0.5). Cumulative percentage will be determined from lowest to highest value. MIC_{50} will be selected as the first value equal to or greater than 50% of organisms. MIC_{90} will be derived in a similar way. The MIC_{50} will only be calculated when ≥5 isolates are available, while the MIC_{90} will only be calculated when ≥10 isolates are available.

Baseline MAC pathogen susceptibility types will be summarized on a by-pathogen and per-patient basis. For each MAC pathogen, susceptible, intermediate, or resistant will be listed for specified antimicrobials according to CLSI interpretive criteria as listed in the M24 Supplement (2023 or later) and Table 1 below. Baseline pathogen will also be categorized as resistant to macrolides, IV amikacin, liposomal inhaled amikacin, moxifloxacin, or specific combinations of these as described in Table 2 below.

Table 1. CLSI Interpretive Criteria for MAC Isolates

	MIC (mg/L)*		
Antimicrobial	**Susceptible**	**Intermediate**	**Resistant**
Clarithromycin	≤8	16	≥32
Amikacin IV	≤16	32	≥64
Amikacin (liposomal, inhaled)	≤64	-	≥128
Moxifloxacin	≤1	2	≥4

*Interpretive Criteria based on CLSI M24 Supplement Edition 2, 2023.

Table 2. Resistant Pathogen Types

Resistance type	Resistant MIC Value*
Macrolide-resistant	Clarithromycin MIC ≥32 mg/L
Amikacin IV-resistant	Amikacin MIC ≥64 mg/L

Resistance type	Resistant MIC Value*
Amikacin (liposomal, inhaled)-resistant	Amikacin MIC ≥128 mg/L
Moxifloxacin	Moxifloxacin MIC ≥4 mg/L
Macrolide and Amikacin IV-resistant	Clarithromycin MIC ≥32 mg/L and Amikacin MIC ≥64 mg/L
Macrolide and Amikacin (liposomal, inhaled)-resistant	Clarithromycin MIC ≥32 mg/L and Amikacin MIC ≥128 mg/L
Macrolide, Amikacin IV, and Moxifloxacin-Resistant	Clarithromycin MIC ≥32 mg/L and Amikacin MIC ≥64 mg/L and Moxifloxacin MIC ≥4 mg/L
Macrolide, Amikacin (liposomal, inhaled), and Moxifloxacin-Resistant	Clarithromycin MIC ≥32 mg/L and Amikacin MIC ≥128 mg/L and Moxifloxacin MIC ≥4 mg/L

*Resistant interpretation based on CLSI M24 Supplement Edition 2, 2023.

Baseline MAC pathogen susceptibility types will be summarized on a by-pathogen and per-patient basis as outlined below:

- By-pathogen summary tables will list genus and species of MAC pathogens by total number of baseline pathogens and by resistance phenotype. Macrolide-, amikacin IV- and inhaled-resistant categories are not mutually exclusive (e.g., a MAC isolate that is macrolide-resistant but amikacin (liposomal, inhaled)-susceptible should still be counted in both summary rows). However, a patient with 2 MAC isolates, one macrolide-resistant and one macrolide-susceptible would be counted only once in the summary rows for macrolide susceptibility type by the highest macrolide MIC.
- Per-patient summary tables will present the total number patients with any resistant pathogen in each category based on the isolate with the highest MIC for the category; e.g., if at least one pathogen isolated in a patient is considered macrolide-resistant type, a patient will be considered having a macrolide-resistant MAC infection).

The distribution of baseline MAC pathogen MIC to all tested antimicrobials will be presented by treatment group and overall for each pathogen/pathogen category for the Micro-ITT Population.

Distribution of epetraborole MICs of MAC pathogens will be produced by resistance phenotype including macrolide-resistant, amikacin IV-resistant, amikacin (liposomal, inhaled)-resistant and the combinations of macrolide and amikacin IV-resistant and macrolide and amikacin (liposomal, inhaled)-resistant.

3.3.5 Medical History and Concomitant Procedures/Non-drug Therapies

Medical history and any concomitant procedures/non-drug therapies will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later. For each System Organ Class (SOC) and preferred term (PT), summaries of prior medical history and concomitant procedures/non-drug therapies will be presented separately by number and percentage of patients having at least one occurrence of a disease or procedure/therapy type. Summaries will be presented by treatment and overall, for all patients in the Safety and Micro-ITT populations.

Listings will be provided for all patients' medical histories and concomitant procedures for the ITT Population.

3.3.6 Prior and Concomitant Medications

For purposes of evaluating inclusion criteria, prior treatment includes all treatment (including over-the-counter treatments such as herbal supplements, vitamins, diet aids, and hormone supplements) received

within the 8 week screening period prior to the date and time of first dose administration of study drug. Any patient record of prior treatment must be documented on the appropriate eCRF.

Concomitant medications or treatments administered between the dates of the first dose of study drug and the last study visit, inclusive, are to be listed on the appropriate eCRF. Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version March 2022G B3 or later version. For summary purposes, medications will be considered prior medications if they were taken at any time within 8 weeks prior to the first dose of study drug and concomitant medications if they were taken at any time on or after the first dose of study drug. Medications started prior to and continued beyond first dose of study drug will be considered both prior and concomitant medications in summaries.

Counts and percentages of patients taking prior and concomitant medications (excluding antibiotics) by ATC class and preferred term will be summarized by treatment and in total based on the Safety Population.

All antibiotics taken in the 12 months prior to screening and through study participation were to be recorded in the antibiotics eCRF, and will be categorized as prior or concomitant and summarized by ATC and preferred term based on the same definitions as for other medications described above. However, antibiotic preferred terms including "salt" suffixes will be consolidated to the base preferred term (e.g. preferred terms of either "Ethambutol" or "Ethambutol dihydrocholoride" will both be mapped to "Ethambutol" for summarization purposes). The summaries for prior and concomitant antibiotics will be further split into antimycobacterial agents administered for MAC lung disease and antibiotics administered for other, non-MAC infections which are potentially effective against MAC and are given for reasons other than clinical failure of study drug. Summaries will be presented by treatment and overall, for all patients in the Safety and Micro-ITT Populations.

3.3.7 Study Drug Exposure

For each study phase, study drug exposure will be summarized in both a Month 6 analysis (all exposures from baseline through Month 6 visit) and final analysis (all exposures from baseline through EOT visit).

The following parameters will be calculated for the exposure data:

- Duration of the oral study drug treatment (days), defined as (the earliest date of Month 6 visit or early discontinuation – date of first treatment + 1) at Month 6 analysis and (date of last confirmed treatment – date of first treatment + 1) at final analysis (through EOT Visit for all patients).
- Compliance (%) for oral study drug will be calculated as actual number of tablets taken/planned number of tablets ×100. Actual number of tablets taken = number of tablets dispensed – returned. Planned number of tablets will be calculated as a sum of all planned doses per intake for a patient.

Study drug compliance checks will be performed by study site or home health care staff by counting the number of remaining tablets in the study drug pill bottles at each study visit. The number of actual tablets taken will be calculated as number of tablets dispensed – number of tablets returned. If study drug is not returned for one or more bottles from a given study visit, the number of tablets expected and actual tablets taken for that visit will be excluded from the compliance calculation. The number of tablets expected will be calculated as the earliest date of Month 6 visit or early discontinuation – date of first dose of study drug +1, multiplied by 2 (i.e., the number of days study drug was expected to be taken x 2 tablets per day) for the Month 6 analysis, and date of last confirmed treatment – date of first dose of study drug +1, multiplied by 2 for the final analysis. Any protocol-directed interruption in study drug use due to adverse events or changes in local laboratory creatinine clearance as recorded in the clinical database will be accounted for by calculating each interruption duration (date of restart – date of last dose prior to interruption – 1)

multiplied by 2, and subtracting these from the denominator prior to calculating overall study drug compliance. Percent compliance to the study drug regimen will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of patients with compliance in the following categories:

- <80%
- 80-100%
- >100%-120%
- >120%

The number and percentage of patients with one or more interruptions in study drug due to changes in creatinine clearance or due to an adverse event (e.g a clinically significant decrease from baseline in hemoglobin), as well as a frequency distribution of the total number of interruptions in study drug due to changes in creatinine clearance or due to an adverse event (0, 1, 2, 3, >3), will be summarized separately by treatment.

The above-defined parameters will be summarized in the Safety Population by treatment arm, both at the Month 6 analysis and for the final analysis. Duration of the oral study drug treatment will be summarized by treatment using descriptive statistics. Compliance will be summarized as a continuous variable.

Listings will be created for all scheduled and unscheduled oral study drug accountability records and derived study drug compliance. Any instances of compliance greater than 100% will be manually confirmed for potential documentation of a study drug overdose and protocol deviation.

For analyses of exposure at the planned Month 6 analysis timepoints in both Phase 2 and Phase 3 of the study, all patients other than those indicating premature discontinuation of study drug prior to Month 6 will be assumed to be on treatment through their date of Month 6 visit, and all study drug accountability records through Month 6 will be incorporated into the above definitions.

3.4 Efficacy Analysis

A primary objective of the Phase 2 part of the study is to assess $MACrO_2$ PRO instrument properties in determining symptom-based clinical response between baseline and Month 3 and baseline and Month 6. The primary objective of the Phase 3 part of the study is to determine if epetraborole + OBR is superior to placebo + OBR in clinical response between baseline and Month 6, as measured by the $MACrO_2$ PRO (pending verification from the Phase 2 part of the study). The other PRO instruments (QOL-B, NTM Symptoms Module, and SGRQ-C) will be incorporated as secondary objectives to assess for symptom/function-based clinical response to oral epetraborole compared to placebo.

As discussed in Section 2.2.6 (Analysis Timing), efficacy analyses will be performed in two stages for Phase 2. However, as the trial was prematurely terminated, only a single overall analysis stage will be performed for Phase 3 after final database lock and unblinding of Phase 3, at which time all efficacy and safety analyses will be performed. The initial stage of analyses will be conducted after the last patient in Phase 2 completes all assessments for the Month 6 visit (including Month 6 +1 week PRO assessments) and all data points though these time points have been entered and cleaned. This will be referred to as the Month 6 Analysis in Phase 2. All efficacy endpoints measured through Month 6 will be assessed at this time and considered final as part of this analysis. Any efficacy endpoint data collected at any visits beyond Month 6 (e.g., EOT, LFU) will not be summarized at the time of this analysis.

The second set of analyses will be conducted after all patients have completed all assessments through end of study and the database has been declared locked for each phase. This will be referred to as the End of

Study Analysis in each phase. All efficacy endpoints based on assessments collected beyond Month 6 in Phase 2 will be assessed at this time and considered final as part of this analysis.

All efficacy endpoints described below will be assessed at exactly one analysis stage (either the Month 6 Analysis or the End of Study Analysis in Phase 2, or in the single End of Study Analysis in Phase 3) and not repeated subsequently, in order to control the type one error level of the overall study conclusions in each phase. As the primary and key secondary endpoints for both US and outside the US regulatory agencies are based on endpoints collected through Month 6 for both Phase 2 and Phase 3, the formal study objectives are expected to be assessed and reported to regulatory authorities at the time of the Month 6 Analysis from Phase 2. All efficacy endpoints assessed at the End of Study Analysis in Phase 2 are identified as additional secondary or exploratory endpoints and are thus considered supportive in nature. Per the revised approach to Phase 3, a single End of Study analysis for all patients in Phase 3 will be performed after the overall study database has been locked, with all endpoints through the LFU visit assessed at this single analysis phase.

The analyses and presentations of Phase 2 data to support the assessment of the measurement properties of the novel $MACrO_2$ PRO and published QOL-B RD score and to provide validation evidence in treatment-refractory NTM lung disease are not included within the SAP, but are outlined in separate Psychometric Analysis Plans (PAPs) for each of the $MACrO_2$ and QOL-B RD PROs. All analyses outlined in this SAP refer to the analyses to estimate the effect of treatment from the Phase 2 data and the Phase 3 data.

It was originally anticipated that the primary endpoint would be $MACrO_2$ PRO symptom-based clinical response at Month 6 for the Phase 3 part of the study (in the US). However, based on review of the overall Phase 2 analysis results along with ongoing advances in PRO literature and other public announcements in this therapeutic area prior to this version of the SAP, the change from baseline to Month 6 in QOL-B respiratory domain score has been chosen as the primary efficacy endpoint in the US in this updated analysis plan. Additionally, as part of the psychometric evaluation of the $MACrO_2$ PRO based on the blinded Phase 2 analysis results along with recommendations received from the FDA's Patient Focused Statistical Scientists (PFSS) reviewers, a new $MACrO_2$ total scaled score (Appendix 8.5) was introduced as an additional secondary efficacy endpoint in the Phase 3 analyses. By-patient sputum culture conversion by Month 6 has been retained as the key secondary endpoint in the US (and primary endpoint outside the US). Formal estimands are provided in the following sections for primary endpoints and key secondary endpoints in each phase, based on these revised endpoints. Due to the change in Phase 3 efficacy endpoints, a revised hierarchical testing order for Phase 3 in the US will be as follows: 1. QOL-B respiratory domain score change from baseline to Month 6 (primary efficacy endpoint in the US); 2. $MACrO_2$ total scaled score change from baseline to Month 6; 3. By-patient sputum culture conversion by Month 6. The revised hierarchical testing order for Phase 3 outside the US will be as follows: 1. By-patient sputum culture conversion by Month 6 (primary efficacy endpoint outside the US); 2. QOL-B respiratory domain score change from baseline to Month 6; MACrO2 total scaled score change from baseline to Month 6.

For each of the three Phase 3 endpoints above, a hierarchical testing approach will be applied, whereby the primary endpoint will be tested, and if superiority is concluded for the primary endpoint, the second and third named endpoints above will then be tested, in order. As no specific claims are intended for other secondary endpoints, no further multiplicity testing will be applied for the other secondary and exploratory endpoints. Furthermore, as any modifications to the Phase 3 primary efficacy or key secondary endpoints in each region are based strictly on data obtained from the fully independent Phase 2 patient analysis population, no adjustment to the overall alpha level of 0.05 for testing the primary efficacy or hierarchically tested secondary endpoints is necessary.

3.4.1 Phase 2 Efficacy Endpoints – Month 6 Analysis

3.4.1.1 Phase 2 Primary Efficacy Endpoint in the US (Secondary Endpoint Outside the US)

The primary efficacy endpoint in the US (secondary outside the US) is symptom-based clinical response assessed by $MACrO_2$ PRO between baseline and Month 3 and baseline and Month 6. While summary results for both of these visits will be generated in parallel, the Month 6 visit will be considered of primary interest with the Month 3 visit considered supportive. The Estimand corresponding to the primary endpoint is defined with the following five attributes:

1. Population: Randomized patients with MAC culture-positive Pre-Study and Screening respiratory specimens
2. Treatment: Epetraborole oral tablets 500 mg (two 250 mg oral tablets) QD + OBR or placebo oral tablets QD matched to epetraborole dosage + OBR
3. Variable: $MACrO_2$ PRO response rate at Month 3 and Month 6. $MACrO_2$ PRO response at the given time point is defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms compared with baseline $MACrO_2$ PRO assessment. The baseline $MACrO_2$ PRO assessment is defined as the last assessment prior to the first dose of study drug.
4. Intercurrent events:
    a. New, additional non-study-specific, antimycobacterial therapy that is potentially effective against MAC for reasons other than clinical failure of study drug: data collected after such therapy will not be used and patients will be classified as a clinical failure for $MACrO_2$ PRO response (composite strategy)
    b. Surgery for MAC lung disease for reasons other than clinical failure of study drug: data collected after such surgery will not be used and patients will be classified as a clinical failure for $MACrO_2$ PRO response (composite strategy)
    c. Permitted medications/interventions or prohibited medications/interventions other than those described in bullets a and b: $MACrO_2$ PRO data collected after permitted or other prohibited medications/interventions administration will be used as recorded (treatment policy strategy)
    d. Inadequate compliance: patient data will be used as recorded (treatment policy strategy)
5. Population-level summary: Difference between epetraborole + OBR and placebo + OBR in response rate in $MACrO_2$ PRO assessment at Month 3 and Month 6.

$MACrO_2$ PRO item scores will be summarized by visit in the Micro-ITT Population, using visits of day 1 (randomization/baseline), Month 3 (day 83 ± 7 days) and Month 6 (day 169 ± 7 days). Summaries of the number and percentage of patients in each severity category (or missing results) for each symptom, by treatment arm and overall for all patients in the Micro-ITT Population, according to patient-reported entries in the $MACrO_2$ PRO, will be produced.

$MACrO_2$ PRO response is defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms. Descriptive statistics (n, %) will be presented by treatment group, along with the treatment difference (i.e. epetraborole + OBR response percentage minus placebo + OBR response percentage), associated 95% confidence interval and p-value, calculated using the method of Miettinen and Nurminen (see Appendix), both including (primary analysis) and excluding (sensitivity analysis) stratification by baseline ALIS use and age (<65 years versus ≥65 years). As the Month 6 visit will be considered of primary interest while the Month 3 result will be considered supportive, no corrections for multiple comparisons are proposed to the corresponding p-values or confidence intervals for these endpoints. As further supportive analyses, corresponding results of the above analyses will be generated in the PP Population.

Patients who receive new, additional non-study-specific, antimycobacterial therapy that is potentially effective against MAC for reasons other than clinical failure of study drug (in treating the index MAC lung infection) will be classified as a clinical failure for the analysis in the Micro-ITT Population and will be excluded from the PP Population. Patients who fail to provide a complete $MACrO_2$ PRO assessment of all symptoms at the specific Month 3 or Month 6 time point will be classified as a clinical failure for the analysis at that time point for all populations.

3.4.1.2 Phase 2 Primary Efficacy Endpoint Outside the US (Secondary Endpoint in the US)

The primary efficacy outside the US (secondary in the US) is by-patient sputum culture conversion monthly through Month 6. The Estimand corresponding to the primary endpoint is defined with the following five attributes:

1. Population: Patients with MAC culture-positive Pre-Study and Screening respiratory specimens
2. Treatment: Epetraborole oral tablets 500 mg (two 250 mg oral tablets) QD + OBR or placebo oral tablets QD matched to epetraborole dosage + OBR
3. Variable: Sputum conversion rate is defined as proportion of patients having culture conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6
4. Intercurrent events:
    a. New, additional non-study-specific, antimycobacterial therapy that is potentially effective against MAC for reasons other than clinical failure of study drug: data collected after such therapy will not be used and patients will be classified as a failure for microbiological response (composite strategy)
    b. Surgery for MAC lung disease for reasons other than clinical failure of study drug: data collected after such surgery will not be used and patients will be classified as a failure for microbiological response (composite strategy)
    c. Permitted medications/interventions or other prohibited medications/interventions other than those described in bullets a and b: microbiological response data collected after permitted or other prohibited medications/interventions administration will be used as recorded (treatment policy strategy)
    d. Inadequate compliance: patient data will be used as recorded (treatment policy strategy)
5. Population-level summary: Difference between epetraborole + OBR and placebo + OBR in sputum conversion rate by Month 6.

"Microbiological response" is defined as sputum culture conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6. By-patient microbiological response will be presented for the Micro-ITT Population by Month 6. Descriptive statistics (n, %) will be presented by treatment group, along with the treatment difference (i.e. epetraborole + OBR response percentage minus placebo + OBR response percentage), associated 95% confidence interval and p-value, calculated using the method of Miettinen and Nurminen, both including (primary analysis) and excluding (sensitivity analysis) stratification by baseline ALIS use and age (<65 years versus ≥65 years).

3.4.1.3 Phase 2 Secondary Efficacy Endpoints at Month 6 Analysis

The secondary efficacy endpoints include microbiological response (by-patient sputum culture conversion and by-patient microbiological improvement) monthly through Month 6, PRO symptom-based clinical response (mean changes in PRO domain scores or improvement of ≥1 grade in the key symptom with no worsening of other symptoms in the $MACrO_2$ PRO) monthly through Month 6, concordance of clinical response and microbiological response (concordance between PRO response and microbiological response), and rates of recurrence, reinfection, and relapse by Month 6.

"Microbiological response" is defined as sputum culture conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6; "microbiological improvement" is defined as a decrease in MAC colony counts of ≥1 category from baseline. By-patient microbiological response by Month 6 and by-patient microbiological improvement at Month 3 and Month 6 (see details below) will be presented for the Micro-ITT Population. Descriptive statistics (n, %) will be presented by visit and treatment group. Treatment difference, associated 95% confidence interval and p-value at Month 3 and Month 6, will be calculated using the method of Miettinen and Nurminen, both including (primary analysis) and excluding (sensitivity analysis) stratification by baseline ALIS use and age (<65 years versus ≥65 years).

By-patient microbiological improvement (decrease in MAC colony counts of ≥1 category from baseline) will be summarized using the categories of 0 = no growth on agar or broth; 1 = growth in broth only; 2 = 1 to 49 CFU/mL; 3 = 50 to 99 CFU/mL; 4 = 100 to 199 CFU/mL; 5 = 200 to 299 CFU/mL; 6 = ≥300 CFU/mL, where specific colony counts are based on solid agar growth. If more than one sputum sample at the same visit is culture positive for the same species of MAC, the culture with the highest colony count will be used for determination of microbiological improvement.

Descriptive statistics of both the reported scores (and change from baseline for continuous scores) will be reported by visit (monthly through Month 6) for scores for all other PROs collected in the study (QOL-B, NTM Symptoms Module, SGRQ-C, PGIS, PGIC, CGIS, CGIC, and Meaningful Change Question) based on the Micro-ITT Population. Change from baseline score at Month 3 and Month 6 of selected continuous PROs including QOL-B respiratory domain score, NTM Symptoms Module domain score, and SGRQ-C total score will be analyzed using an analysis of covariance (ANCOVA) model, including baseline score, treatment and stratification factors (baseline ALIS use and age (<65 years versus ≥65 years)) as covariates. Least squares means, 95% confidence intervals, and p-values of the treatment comparison will be presented for both Micro-ITT and PP populations.

Clinical response as defined above for the $MACrO_2$ PRO as well as for each additional PRO measure according to pre-defined response thresholds relative to baseline will be examined monthly through Month 6. Response in QOL-B respiratory domain score is defined as an improvement in QOL-B respiratory domain score of ≥8 based on a minimally clinically important difference (MCID) established for bronchiectasis patients (Quittner 2015b), as well as by a threshold to be determined as part of a blinded anchor-based psychometric analysis of the observed QOL-B respiratory domain scores across pooled treatment arms and visits as a potentially more specific indicator of meaningful improvement in treatment-refractory MAC patients. Response in SGRQ-C total score is defined as an improvement in SGRQ-C total score of ≥4 based on a MCID established for COPD patients (Jones 2023). A corresponding threshold for a response endpoint in the NTM Symptoms domain of the NTM Module has not been defined, as an MCID has yet to clearly established for this endpoint, but this study will investigate distribution-based minimal important differences (MIDs) using 0.5 × baseline SD and the standard error of the mean (SEM) of the baseline measurement, where in both cases baseline is pooled across both treatment groups in the Micro-ITT Population, as experimental response thresholds. Response in PGIS or CGIS at each post-baseline visit is defined as a reduction in severity of one or more grades relative to baseline. Response in PGIC or CGIC at each post-baseline visit is defined as a reported change of severity category of "Much Better" or "A Little Better." For all of the above PRO response definitions, missing results at the given timepoint will be considered failures in the Micro-ITT analysis.

Clinical response as defined above for each individual PRO endpoint ($MACrO_2$, QOL-B respiratory domain, SGRQ-C, NTM Symptoms Module, PGIS, CGIS, PGIC, and CGIC) will be presented dichotomously (Yes/No) for each treatment arm and will be presented as the treatment difference and associated 95% confidence interval and p-value, calculated using the method of Miettinen and Nurminen

stratified by baseline ALIS use and age (<65 years versus ≥65 years) for both the Micro-ITT and PP populations. In addition, to examine the influence of baseline severity on the treatment effect, clinical response rate by month will also be analyzed using a logistic regression model, including treatment and baseline key symptom severity (for $MACrO_2$ only), baseline score (for QOL-B respiratory domain, SGRG-C Total Score, NTM Symptoms Domain), baseline severity in CGIS (for CGIS and CGIC), or baseline severity in PGIS (for PGIS and PGIC) as covariates. Stratification factors of baseline ALIS use and age (<65 years versus ≥65 years) will also be included as covariates in each model. For each logistic regression model, the estimated odds ratio and 95% confidence interval and corresponding p-value for the treatment effect will be presented.

Line plots of mean score (+/- SD) over time will be produced for continuous PROs (e.g., QOL-B domain score, NTM symptom module score and total SGRQ-C score), with the two treatment groups indicated with different colors on the plot. A bar plot of categorical PROs (e.g., proportion of $MACrO_2$ responders, individual and key $MACrO_2$ symptoms, PGIS, PGIC, CGIS, CGIC and Meaningful Change Question) by treatment group will also be produced by visit.

In order to assess the concordance of PRO changes with microbiological changes the following summaries will be produced for each PRO in the Micro-ITT Population. These will be produced at Months 3 and 6, as specifically noted below:

- Summary of PRO response (Response/Failure) versus sputum culture conversion (Conversion/No Conversion) by Month 6
- Summary of PRO response (Response/Failure) at Month 3 versus sputum culture conversion (Conversion/No Conversion) by Month 6
- Summary of PRO response (Response/Failure) versus microbiological improvement (Improvement/No Improvement/Non Applicable Due to Missing Baseline CFU Score) at Months 3 and 6
- Summary of PRO response (Response/Failure) versus microbiological colony count culture categories (Missing, 0, 1, 2, 3, 4, 5, 6) at Months 3 and 6

Rates of recurrence, relapse, and reinfection following two different definitions will be presented by Month 6 in the Micro-ITT Population. The primary analysis of recurrence, relapse, and reinfection will use the following definitions derived from the NTM-NET consensus statement (van Ingen 2018) regarding treatment outcome definitions in NTM pulmonary disease:

- Recurrence is defined as at least 1 MAC-positive culture on any media type (broth or agar) for 2 consecutive visits after culture conversion. Recurrence will be further categorized as either reinfection or relapse as follows:
  - Re-infection: at least 1 MAC-positive culture of a different species or the same species but a different strain of the causative species for 2 consective visits after culture conversion
  - Relapse: at least 1 MAC-positive culture of the same strain as the causative species for 2 consecutive visits after culture conversion

A sensitivity analysis will also be performed using the following definitions from the CONVERT trial (Griffith 2021):

- Recurrence is defined as having MAC-positive sputum cultures after culture conversion in liquid broth media (agar negative) for 3 or more consecutive visits, or having 1 MAC-positive sputum culture on solid media (LJ and/or 7H11 agar positive). Recurrence will be further categorized as either reinfection or relapse as follows:
  - Reinfection: new infection with a different MAC species or the same MAC species but a different strain from that isolated at baseline
  - Relapse: same MAC species and strain that was isolated at baseline

At the time of Month 6 database lock, only overall recurrence rates by either definition will be presented. Further subdivision into relapse verus reinfection within each definition of recurrence will be determined by whole genome sequencing when available. Identification of the overall recurrence, reinfection and relapse will be determined by a Sponsor Pathogen Review Committee in accordance with the Pathogen Review Plan.

3.4.1.4 Phase 2 Exploratory Efficacy Endpoints at Month 6 Analysis

In an exploratory analysis, descriptive statistics for clinical response and microbiological response (by-patient sputum culture conversion and by-patient microbiological improvement) at Month 3 (as applicable) and Month 6 will be presented by age category, ALIS use at baseline, presence-absence of any fibrocavitary disease, chest cavity category (non-cavitary, cavity diameter ≤ 3 cm, cavity diameter > 3 cm from EDC), MAC resistance phenotype (ie, macrolide-resistant, amikacin IV-resistant, and amikacin (liposomal, inhaled)-resistant), sex, baseline creatinine clearance category (<60 mL/min, ≥60 mL/min to <90 mL/min, or ≥ 90 mL/min), BMI category (<18.5 vs ≥18.5 kg/m^2), and country of enrollment in the Micro-ITT Population. Forest plots of response by treatment group will be presented across all subsets, but no formal statistical testing will be performed.

Radiographic response at Month 6, defined as overall change from baseline based on blinded central reading of chest CT will be summarized at Month 6 and the proportion of patients meeting the criteria of overall improvement from baseline (Y/N; with Yes defined as those categorized as either "Resolution" or "Improvement", and No as all other categories or missing interpretation) will be presented by treatment group, along with the treatment difference and associated 95% confidence interval, calculated using the method of Miettinen and Nurminen, including stratification by baseline ALIS use and age (<65 years versus ≥65 years) in the Micro-ITT Population.

By-patient sputum culture conversion by Month 6 and by-patient microbiological improvement at Month 3 and Month 6 by epetraborole MIC across all baseline pathogens and within each individual baseline pathogen species will be summarized by treatment group in the Micro-ITT Population. By-pathogen microbiological sputum culture conversion by Month 6 and by-pathogen microbiological improvement at Month 3 and Month 6 will be summarized by treatment group for each individual baseline pathogen in the Micro-ITT Population.

Time (in days) to first sustained $MACrO_2$ PRO-based clinical response through Month 6 will be summarized by treatment group in the Micro-ITT Population. The first sustained PRO-based clinical response through Month 6 is defined as the earliest study day at which the weekly $MACrO_2$ assessment meets the criteria of clinical response and which is maintained consistently at all available subsequent assessments through Month 6 (inclusive). Missing assessments will be excluded from sustained response determination. A Kaplan-Meier analysis and corresponding plot will be provided by treatment, and estimated event rates by treatment arm based on the plot will be provided for study days 29, 57, 85, 113, 141, and 169 to align with protocol specified visit months. Patients who fail to achieve sustained response

by Month 6 or discontinue early from the study will be censored at their last day of treatment or the day of their Month 6 visit, whichever is earlier. In an alternative approach to assess the impact of censoring on the analysis results, the same analysis will be performed where all patients who fail to achieve sustained response and who discontinue from the study prior to Month 6 will be censored at the maximum allowable duration of 6 Months. Time to event will also be analyzed using a Cox proportional hazard model with the same variables as the previous exploratory analysis, and hazard ratio and 95% confidence intervals at Month 6 will be reported.

Time (in months) to first negative sputum culture through Month 4 will be summarized by treatment group in the Micro-ITT Population. A Kaplan-Meier analysis and corresponding plot will be provided by treatment, and estimated event rates by treatment arm based on the plot will be provided for months 1 (Day 29), 2 (Day 57), 3 (Day 85), and 4 (Day 113). Patients who fail to achieve the endpoint by Month 4 or discontinue early from the study will be censored at their last day of treatment or the day of their Month 4 visit, whichever is earlier. In an alternative approach to assess the impact of censoring on the analysis results, the same analysis will be performed where all patients who fail to achieve the endpoint and who discontinue from the study prior to Month 4 will be censored at the maximum allowable duration of 4 Months. Time to event will also be analyzed using a Cox proportional hazard model with the same variables as the previous exploratory analysis, and hazard ratio and 95% confidence intervals at Month 4 will be reported.

Time (in months) to first sustained decrease from baseline in MAC colony counts by ≥1 category through Month 6 will be summarized by treatment group in the Micro-ITT Population. The first sustained decrease from baseline in colony count category through Month 6 is defined as the earliest monthly visit at which the definition of microbiological improvement is met and and which is met consistently at all available subsequent visits through Month 6 (inclusive). Patients with missing baseline colony count will be excluded from the analysis. However, any visits with confirmation of no growth of the baseline pathogen will be considered improvement relative to baseline. A Kaplan-Meier analysis and corresponding plot will be provided by treatment, and estimated event rates by treatment arm based on the plot will be provided for months 1 (Day 29) through 6 (Day 169). Patients who fail to achieve the endpoint by Month 6 or discontinue early from the study will be censored at their last day of treatment or the day of their Month 6 visit, whichever is earlier. In an alternative approach to assess the impact of censoring on the analysis results, the same analysis will be performed where all patients who fail to achieve the endpoint and who discontinue from the study prior to Month 6 will be censored at the maximum allowable duration of 6 Months. Time to event will also be analyzed using a Cox proportional hazard model with the same variables as the previous exploratory analysis, and hazard ratio and 95% confidence intervals at Month 6 will be reported.

3.4.2 Phase 2 Efficacy Endpoints – End of Study Analysis

3.4.2.1 Phase 2 Secondary Efficacy Endpoints at End of Study Analysis

The secondary efficacy endpoints include rates of recurrence, reinfection, and relapse by End of Therapy and Late Follow-up. Rates of recurrence based on the definitions included in Section 3.4.1.3 will be presented by EOT and LFU in the Micro-ITT Population. Further subdivision into relapse versus reinfection within each definition of recurrence will be determined by whole genome sequencing prior to database lock.

3.4.2.2 Phase 2 Exploratory Efficacy Endpoints at End of Study Analysis

Radiographic response at EOT, defined as overall change from baseline based on blinded central reading of chest CT will be summarized at baseline and at EOT and the proportion of patients meeting the criteria of overall improvement from baseline (Y/N; with Yes defined as those categorized as either “Resolution”

or "Improvement", and No as all other categories or missing interpretation) will be presented by treatment group, along with the treatment difference and associated 95% confidence interval, calculated using the method of Miettinen and Nurminen, including stratification by baseline ALIS use and age (<65 years versus ≥65 years) in the Micro-ITT Population.

Rate of decreased susceptibility among postbaseline MAC isolates, defined as a ≥4-fold increase in epetraborole MIC relative to the baseline isolate MIC at any post-baseline follow-up visit, among patients remaining MAC culture-positive at Month 4 or later will be summarized by treatment group in the Micro-ITT Population. Rates of decreased clarithromycin or IV amikacin susceptibility, defined as a change from interpretation of Susceptible or Intermediate at baseline to Resistant at any post-baseline follow-up visit according to the interpretive criteria provided in Table 1, will be summarized similarly. All patients meeting the criteria for decreased susceptibility for any of the above drugs will be presented in a listing with all individual drug panel MICs provided by visit to support review of their trends over time.

Up to 40 eligible patients in the Phase 2 part of the study will participate in an optional qualitative embedded interview to share their experience in the study. During the interviews, patients will be asked to discuss how each of their symptoms improved, worsened, or remained the same, and whether those changes were meaningful, using the $MACrO_2$ PRO to anchor the discussion. Results from the embedded interviews will be used to inform or confirm the symptom-based clinical response definition in the analysis plan for the Phase 3 endpoints. All interviewers will be blind to the patient's treatment allocation. The summarization of these embedded interview findings will be described in separate Qualitative Analysis Plan.

3.4.3 Phase 3 Efficacy Endpoints

3.4.3.1 Phase 3 Primary Efficacy Endpoint in the US (Key Secondary Endpoint Outside the US)

The primary efficacy endpoint in the US (key secondary outside the US) is change from baseline to Month 6 in QOL-B respiratory domain score. The Estimand corresponding to the primary endpoint is defined with the following five attributes:

1. Population: Patients with MAC culture-positive Pre-Study and Screening respiratory specimens
2. Treatment: Epetraborole oral tablets 500 mg (two 250 mg oral tablets) QD + OBR or placebo oral tablets QD matched to epetraborole dosage + OBR
3. Variable: Change from baseline to Month 6 in QOL-B respiratory domain score. QOL-B respiratory domain score is measured on a scale from 0 to 100 (with higher scores indicating better health-related quality of life). The baseline QOL-B respiratory domain score assessment is defined as the last entry recorded or updated by the patient on or prior to the first dose of study drug + 1 day (ePRO-specified close of window to further entry to patients).
4. Intercurrent events:
    a. New, additional non-study-specific, antimycobacterial therapy that is potentially effective against MAC for reasons other than clinical failure of study drug: data collected after such therapy will be set to the last available score from a visit prior to the start of therapy (composite strategy)
    b. Surgery for MAC lung disease for reasons other than clinical failure of study drug: data collected after such surgery will not be used and results will be set to the last available score from a visit prior to surgery (composite strategy)
    c. Permitted medications/interventions or prohibited medications/interventions other than those described in bullets a and b: QOL-B respiratory domain data collected after permitted or other prohibited medications/interventions administration will be used as recorded (treatment policy strategy)
    d. Inadequate compliance: patient data will be used as recorded (treatment policy strategy)

5. Population-level summary: Difference between epetraborole + OBR and placebo + OBR in least squares mean change from baseline to Month 6 in QOL-B respiratory domain score.

QOL-B respiratory domain scores are measured on a scale from 0 to 100 (with higher scores indicating better health-related quality of life). QOL-B respiratory domain scores will be summarized by visit in the Micro-ITT Population. Descriptive statistics of both the reported QOL-B respiratory domain scores and change from baseline will be reported by visit (monthly through Month 6). Change from baseline to Month 6 in QOL-B respiratory domain score will be analyzed using an analysis of covariance (ANCOVA) model, including baseline score, treatment and either including (primary analysis) or excluding (sensitivity analysis 1) stratification factors of baseline ALIS use and the presence or absence of any fibrocavitary disease as covariates. Least squares means, 95% confidence intervals, and p-values of the treatment comparison will be presented for both the Micro-ITT (primary) and PP (sensitivity) populations.

Patients who fail to provide a complete QOL-B respiratory domain score at both baseline and Month 6 will be excluded from the analysis and considered unbiased under the missing at random (MAR) assumption, with the exception of patients experiencing intercurrent events, which will be accounted for following the imputation rules above. However, in an additional pair of sensitivity analyses, the primary efficacy analysis will be repeated as described above, but applying a treatment policy strategy in which results for patients with new, additional non-study-specific, antimycobacterial therapy that is potentially effective against MAC, or surgery for MAC lung disease, for reasons other than clinical failure of study drug, will be used as recorded. These models will be run using the ANCOVA model as described above, including baseline score, treatment and either including (sensitivity analysis 2) or excluding (sensitivity analysis 3) stratification factors of baseline ALIS use and the presence or absence of any fibrocavitary disease as covariates.

3.4.3.2 Phase 3 Primary Efficacy Endpoint Outside the US (Key Secondary Endpoint in the US)

The primary efficacy outside the US (secondary in the US) is by-patient sputum culture conversion monthly through Month 6. The Estimand corresponding to the primary endpoint is defined with the following five attributes:

1. Population: Patients with MAC culture-positive Pre-Study and Screening respiratory specimens
2. Treatment: Epetraborole oral tablets 500 mg (two 250 mg oral tablets) QD + OBR or placebo oral tablets QD matched to epetraborole dosage + OBR
3. Variable: Sputum conversion rate is defined as proportion of patients having culture conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6
4. Intercurrent events:
    a. New, additional non-study-specific, antimycobacterial therapy that is potentially effective against MAC for reasons other than clinical failure of study drug: data collected after such therapy will not be used and patients will be classified as a failure for microbiological response (composite strategy)
    b. Surgery for MAC lung disease for reasons other than clinical failure of study drug: data collected after such surgery will not be used and patients will be classified as a failure for microbiological response (composite strategy)
    c. Permitted medications/interventions and or prohibited medications/interventions other than those described in bullets a and b: microbiological response data collected after permitted or other prohibited medications/interventions administration will be used as recorded (treatment policy strategy)
    d. Inadequate compliance: patient data will be used as recorded (treatment policy strategy)

5. Population-level summary: Difference between epetraborole + OBR and placebo + OBR in sputum conversion rate by Month 6.

"Microbiological response" is defined as sputum culture conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6. By-patient microbiological response will be presented for the Micro-ITT Population by Month 6. Descriptive statistics (n, %) will be presented by treatment group, along with the treatment difference (i.e. epetraborole + OBR response percentage minus placebo + OBR response percentage), associated 95% confidence interval and p-value, calculated using the method of Miettinen and Nurminen, both including (primary analysis) and excluding (sensitivity analysis) stratification by baseline ALIS use and the presence or absence of any fibrocavitary disease.

3.4.3.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints include microbiological response (by-patient sputum culture conversion monthly through Month 6 and by-patient microbiological improvement at Month 3 and Month 6), PRO symptom-based clinical response (mean changes in PRO domain scores or improvement of ≥1 grade in the key symptom with no worsening of other symptoms in the $MACrO_2$ PRO) monthly through Month 6, concordance of clinical response and microbiological response (concordance between PRO response and microbiological response), and rates of recurrence, reinfection, and relapse by Month 6.

"Microbiological response" is defined as sputum culture conversion based on 3 consecutive monthly negative sputum cultures for MAC by Month 6; "microbiological improvement" is defined as a decrease in MAC colony counts of ≥1 category from baseline. By-patient microbiological response at Months 6 and by-patient microbiological improvement by Month 3 and Month 6 will be presented for the Micro-ITT Population. Descriptive statistics (n, %) will be presented by visit and treatment group. Treatment difference, associated 95% confidence interval and p-value at Month 3 and 6, will be calculated using the method of Miettinen and Nurminen, both including (primary analysis) and excluding (sensitivity analysis) stratification by baseline use of ALIS and the presence or absence of any fibrocavitary disease.

By-patient microbiological improvement (decrease in MAC colony counts of ≥1 category from baseline) will be summarized using the categories of 0 = no growth on agar or broth; 1 = growth in broth only; 2 = 1 to 49 CFU/mL; 3 = 50 to 99 CFU/mL; 4 = 100 to 199 CFU/mL; 5 = 200 to 299 CFU/mL; 6 = ≥300 CFU/mL. If more than one sputum sample at the same visit is culture positive for the same species of MAC, the culture with the highest colony count will be used for determination of microbiological improvement.

Descriptive statistics of both the reported scores and change from baseline (for continuous scores only) will be reported by visit (monthly through Month 6) for scores for all PROs collected in the study (QOL-B domain scores, $MACrO_2$ total scaled score, NTM Symptoms Module, SGRQ-C, PGIS, PGIC, CGIS, CGIC, and Meaningful Change Question) based on the Micro-ITT Populations. Change from baseline score at Month 3 and Month 6 of selected continuous PROs including QOL-B respiratory domain score (Month 3 only, as Month 6 is the primary efficacy analysis), $MACrO_2$ total scaled score, NTM Symptoms Module domain score, and SGRQ-C total score will be analyzed using an analysis of covariance (ANCOVA) model, including baseline score, treatment and stratification factors (baseline ALIS use and presence or absence of any fibrocavitary disease) as covariates. Least squares means, 95% confidence intervals, and p-values of the treatment comparison will be presented for both Micro-ITT and PP populations. Intercurrent events will be handled following the same rules as for the primary efficacy analysis.

Clinical response as defined above for the $MACrO_2$ PRO as well as for each additional PRO measure according to pre-defined response thresholds relative to baseline will be examined monthly through Month 6. $MACrO_2$ original responder is defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms. Response in QOL-B respiratory domain score is defined as an improvement

in QOL-B respiratory domain score of ≥8 based on a minimally clinically important difference (MCID) established for bronchiectasis patients (Quittner 2015b), as well as by a threshold (11.1 points) determined as part of a blinded anchor-based psychometric analysis of the observed QOL-B respiratory domain scores from Phase 2 patients across pooled treatment arms and visits as a potentially more specific indicator of meaningful improvement in treatment-refractory MAC patients. Similarly, response in $MACrO_2$ total scaled score is defined as an improvement (decrease in total score) by a threshold (11.3 points) determined as part of a blinded anchor-based psychometric analysis of the observed total scaled scores from Phase 2 patients across pooled treatment arms and visits as an indicator of holistic symptom-based improvement in treatment-refractory MAC patients. Response in SGRQ-C total score is defined as an improvement in SGRQ-C total score of ≥4 based on a MCID established for COPD patients (Jones 2023). A corresponding threshold for a response endpoint in the NTM Symptoms domain of the NTM Module has not been defined, as an MCID has yet to clearly established for this endpoint, but this study will investigate distribution-based minimal important differences (MIDs) using 0.5 × baseline SD and the standard error of the mean (SEM) of the baseline measurement, where in both cases baseline is pooled across both treatment groups in the Micro-ITT Population, as experimental response thresholds. Response in PGIS or CGIS at each post-baseline visit is defined as a reduction in severity of one or more grades relative to baseline. Response in PGIC or CGIC at each post-baseline visit is defined as a reported change of severity category of "Much Better" or "A Little Better." For all of the above PRO response definitions, missing results at the given timepoint will be considered failures in the Micro-ITT analysis.

Clinical response as defined above for each individual PRO endpoint point (QOL-B respiratory domain, $MACrO_2$ original responder definition and response in total scaled score by threshold, SGRQ-C, NTM Symptoms Module, PGIS, CGIS, PGIC, and CGIC) will be presented dichotomously (Yes/No) for each treatment arm and will be presented as the treatment difference and associated 95% confidence interval and p-value, calculated using the method of Miettinen and Nurminen stratified by baseline use of ALIS and the presence or absence of any fibrocavitary disease for both the Micro-ITT and PP populations. In addition, to examine the influence of baseline severity on the treatment effect, clinical response rate by month will also be analyzed using a logistic regression model, including treatment and baseline key symptom severity (for $MACrO_2$ original responder definition only), baseline score (for QOL-B respiratory domain, $MACrO_2$ total scaled score, SGRG-C Total Score, NTM Symptoms Domain), baseline severity in CGIS (for CGIS and CGIC), or baseline severity in PGIS (for PGIS and PGIC) as covariates. Stratification factors of baseline ALIS use and the presence or absence of any fibrocavitary disease will also be included as covariates in each model. For each logistic regression model, the estimated odds ratio and 95% confidence interval and corresponding p-value for the treatment effect will be presented.

Line plots of mean score (+/- SD) as well as mean (+/- SD) change from baseline in score over time will be produced for continuous PROs (e.g., QOL-B domain scores, $MACrO_2$ total scaled score, NTM symptom module score and total SGRQ-C score), with the two treatment groups indicated with different colors on the plot. A bar plot of categorical PROs (e.g., proportion of $MACrO_2$ responders, PGIS, PGIC, CGIS, CGIC and Meaningful Change Question) by treatment group will also be produced by visit.

In order to assess the concordance of PRO changes with microbiological changes the following summaries will be produced for each PRO. These will be produced at Month 3 and 6, as specifically noted below:

- Summary of PRO response (Response/Failure) versus sputum culture conversion (Conversion/No Conversion) by Month 6
- Summary of PRO response (Response/Failure) at Month 3 versus sputum culture conversion (Conversion/No Conversion) by Month 6

- Summary of PRO response (Response/Failure) versus microbiological improvement (Improvement/No Improvement/Non Applicable Due to Missing Baseline CFU Score)
- Summary of PRO response (Response/Failure) versus microbiological colony count culture categories (Missing, 0, 1, 2, 3, 4, 5, 6)
- Scatterplots of colony count category versus change from baseline in continuous PRO score, by treatment and by visit (Month 3 and Month 6)

Rates of microbiological recurrence, relapse, and reinfection following two different definitions will be presented by Month 6, by End of Therapy Visit, and by Late Follow-up Visit in the Micro-ITT Population. The primary analysis of recurrence, relapse, and reinfection will use the following definitions derived from the NTM-NET consensus statement (van Ingen 2018) regarding treatment outcome definitions in NTM pulmonary disease:

- Recurrence is defined as at least 1 MAC-positive culture on any media type (broth or agar) for 2 consecutive visits after culture conversion. Recurrence will be further categorized as either reinfection or relapse as follows:
  - Re-infection: at least 1 MAC-positive culture of a different species or the same species but a different strain of the causative species for 2 consective visits after culture conversion
  - Relapse: at least 1 MAC-positive culture of the same strain as the causative species for 2 consecutive visits after culture conversion

A sensitivity analysis will also be performed using the following definitions from the CONVERT trial (Griffith 2021):

- Recurrence is defined as having MAC-positive sputum cultures after culture conversion in liquid broth media (agar negative) for 3 or more consecutive visits, or having 1 MAC-positive sputum culture on solid media (LJ and/or 7H11 agar positive). Recurrence will be further categorized as either reinfection or relapse as follows:
  - Reinfection: new infection with a different MAC species or the same MAC species but a different strain from that isolated at baseline
  - Relapse: same MAC species and strain that was isolated at baseline

Subdivision into relapse verus reinfection within each definition of recurrence will be determined by whole genome sequencing when available. Identification of the overall recurrence, reinfection and relapse will be determined by a Sponsor Pathogen Review Committee in accordance with the Pathogen Review Plan.

3.4.3.4 Phase 3 Exploratory Efficacy Endpoints

In an exploratory analysis, descriptive statistics for least-square mean difference of change from baseline in QOL-B respiratory domain score and $MACrO_2$ total scaled score, and by-patient sputum culture conversion by Month 6 will be presented by age category, ALIS use at baseline, presence-absence of any fibrocavitary disease, chest cavity category (non-cavitary, cavity diameter $\leq$ 3 cm, cavity diameter > 3 cm from EDC), MAC resistance phenotype (ie, macrolide-resistant, amikacin IV-resistant, and amikacin (liposomal, inhaled)-resistant), sex, baseline creatinine clearance category (<60 mL/min, ≥60 mL/min to <90 mL/min, or ≥ 90 mL/min), BMI category (<18.5 vs ≥18.5 kg/m^2), and country of enrollment in the Micro-ITT Population. Forest plots of the estimated treatment difference and 95% confidence interval will be presented across all subsets, but no formal statistical testing will be performed.

Change from baseline in continuous PROs, including QOL-B respiratory domain score, $MACrO_2$ total scaled score, NTM Symptoms Module Domain score, and SGRQ-C total score, will be analyzed using a mixed model for repeated measures (MMRM) that includes randomized treatment, visit (from Baseline to Month 6 inclusive), and treatment by visit interaction as explanatory variables, and corresponding baseline score as a continuous covariate. Treatment visit and treatment by visit interaction will be fixed effects in the model, and treatment by visit interaction will remain in the model regardless of significance. The participant effect will be fitted as a random effect and an unstructured covariance structure will be assumed for within participant variation. If this model does not converge then the covariance matrices of Toeplitz, first-order autoregressive, and compound symmetry will be used in that order until the model converges. The analysis will be performed using PROC MIXED in SAS and the resulting F-tests will be based on Kenward-Roger's adjusted degrees of freedom. Least squares means, 95% confidence intervals, and p-values of the treatment comparisons at Month 3 and Month 6 will be presented for both Micro-ITT and PP populations, along with an assessment of the difference between slopes from baseline to Month 6 and residual plots will be provided to examine departures from normality and/or outliers.

By-patient sputum culture conversion by Month 6 and by-patient microbiological improvement at Month 3 and Month 6 by epetraborole MIC across all baseline pathogens and within each individual baseline pathogen species will be summarized by treatment group in the Micro-ITT Population. By-pathogen microbiological sputum culture conversion at Month 6 and by-pathogen microbiological improvement at Month 3 and Month 6 will be summarized by treatment group for each individual baseline pathogen in the Micro-ITT Population.

Time (in days) to first sustained improvement in QOL-B respiratory domain score by a threshold (11.1 points) determined as part of a blinded anchor-based psychometric analysis of pooled Phase 2 data, time (in days) to first sustained $MACrO_2$ PRO-based clinical response through Month 6, and time to first sustained improvement in MACrO2 total scaled score by a threshold (11.3 points) determined as part of a blinded anchor-based psychometric analysis of pooled Phase 2 data will be summarized by treatment group in the Micro-ITT Population. The first sustained PRO-based clinical response through Month 6 is defined as the earliest study day at which the weekly (or monthly) PRO assessment meets the criteria of clinical response and which is maintained consistently at all available subsequent assessments through Month 6 (inclusive). Missing assessments will be excluded from sustained response determination. A Kaplan-Meier analysis and corresponding plot will be provided by treatment, and estimated event rates by treatment arm based on the plot will be provided for study days 29, 57, 85, 113, 141, and 169 to align with protocol specified visit months. Patients who fail to achieve sustained response by Month 6 or discontinue early from the study will be censored at their last day of treatment or the day of their Month 6 visit, whichever is earlier. In an alternative approach to assess the impact of censoring on the analysis results, the same analysis will be performed where all patients who fail to achieve sustained response and who discontinue from the study prior to Month 6 will be censored at the maximum allowable duration of 6 Months. Time to event will also be analyzed using a Cox proportional hazard model with the same variables as the previous exploratory analysis, and hazard ratio and 95% confidence intervals at Month 6 will be reported.

Radiographic response at Month 6 and at EOT, defined as overall change from baseline based on blinded central reading of chest CT will be summarized at baseline and at Month 6 and at EOT and the proportion of patients meeting the criteria of overall improvement from baseline (Y/N; with Yes defined as those categorized as either "Resolution" or "Improvement", and No as all other categories or missing interpretation) will be presented by treatment group, along with the treatment difference and associated 95% confidence interval, calculated using the method of Miettinen and Nurminen, including stratification by baseline ALIS use and presence or absence of any fibrocavitary disease in the Micro-ITT Population.

Rate of decreased susceptibility among postbaseline MAC isolates, defined as a ≥4-fold increase in epetraborole MIC relative to the baseline isolate MIC at any post-baseline follow-up visit, among patients remaining MAC culture-positive at Month 4 or later will be summarized by treatment group in the Micro-ITT Population. Rates of decreased clarithromycin or IV amikacin susceptibility, defined as a change from interpretation of Susceptible or Intermediate at baseline to Resistant at any post-baseline follow-up visit according to the interpretive criteria provided in Table 1, will be summarized similarly.

3.5 Safety Analysis

Safety data will be summarized by actual treatment received (and in total for selected analyses) as a primary endpoint in Phase 2 and a secondary endpoint in Phase 3 based on the Safety Population. All the analyses in this section will be run on the Safety Population of each study phase, and will be generated separately for all safety data collected through the Month 6 visit and again for all safety data collected through the end of study in Phase 2, while a single analysis of safety through the end of study will be generated for Phase 3. Safety data across the Phase 2 and 3 Safety populations will not be pooled as part of this analysis plan. No hypothesis testing will be performed; all analyses will be descriptive in nature.

Assessments of safety will include the following:

- Assessment of TEAEs;
- Changes from baseline and in laboratory tests (including chemistry, hematology, and urinalysis parameters), including shifts in severity grade or relative to normal ranges for selected laboratory parameters;
- Changes from baseline in vital signs; and
- Change from baseline in 12-lead ECG parameters.

3.5.1 Treatment-emergent Adverse Events (TEAEs)

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product (IMP), whether or not related to the IMP. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. SAEs occurring from the time of informed consent through LFU will be collected. For non-serious AEs, TEAEs are defined as AEs that started from the time of the first dose of study drug through EOT; for serious AEs, TEAEs are defined as SAEs that started from the time of the first dose of study drug through LFU.

Investigators will monitor each patient for clinical and laboratory evidence for pre-defined AEs of special interest (AESIs) through LFU.

For this study, gastrointestinal intolerance, anemia, and (added prior to the Phase 3 analysis only) pneumonitis are considered AESIs. During the course of the study, additional AESIs may be identified by the Sponsor, and will be documented to support safety analyses at each analysis time point. A list of preferred terms to be included as AESIs by category will be finalized by the Sponsor prior to database lock and unblinding of each planned analysis.

AESIs related to gastrointestinal intolerance include, but are not limited to:

- *C. difficile* colitis

- Pseudomembranous colitis
- *C. difficile* test positive
- Diarrhea
- Nausea
- Vomiting

AESIs related to anemia include, but are not limited to:

- Anemia
- Aplastic anemia
- Coombs negative hemolytic anemia
- Coombs positive hemolytic anemia
- Hematocrit decreased
- Hemoglobin decreased
- Hemolysis
- Hemolytic anemia
- Intravascular hemolysis
- RBC decreased

AESIs related to pneumonitis (for Phase 3 only) included, but are not limited to:

- Pneumonitis
- Hypersensitivity pneumonitis
- Interstitial lung disease
- Pulmonary toxicity

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related (definitely related, probably related, and possibly related) TEAEs (overall and by maximum severity)
- Any treatment-emergent AESIs (overall and by maximum severity, as well as by specific AESI category as described above)
- Any serious AEs (SAEs)
- Any TEAEs related to COVID-19
- Any treatment-emergent SAEs
- Any study drug related treatment-emergent SAEs
- Any TEAEs leading to premature discontinuation of study drug
- Any TEAEs leading to study drug interruption
- Any TEAEs of Grade 3 anemia or worse leading to study drug interruption
- Any AEs leading to death

Counts and percentages of patients will also be presented by SOC (or AESI category) and PT for each of the categories listed in the overview. Summaries of all TEAEs, all study drug related TEAEs, and all SAEs by decreasing frequency of PT for epetraborole will also be provided by treatment and overall. Based on version 25.0 or later of MedDRA, AEs reported due to COVID-19 will be appropriately coded in the listings and identifiable in the summary tables and listings by SOC and PT.

AE summaries will include the number of patients with a given AE, as well as the number of AEs themselves.

For all summaries, patients will be counted once for each AE category, SOC, or individual AE PT. For the summaries by severity grade, every patient will be counted once for each AE at the highest severity.

An overview of AEs in the format described above will be provided for key subgroups of interest, including age category, sex, geographic region and country, baseline creatinine clearance category (<60 mL/min, ≥60 mL/min to <90 mL/min, or ≥ 90 mL/min), and baseline BMI category (<18.5 vs ≥18.5 kg/m^2).

Additionally, an overview of AEs listing all categories described above will be provided after adjusting for total patient-years of exposure. Incidence rates will be calculated as the number of patients who experienced one or more events in each category during the specific study duration (through Month 6 or overall), divided by the sum of the number of years of exposure across all exposed subjects in each treatment arm. Total years of exposure will be based on the duration of exposure (in days) calculated for each patient as defined in Section 3.3.7, divided by 365.25 days, and rounded to the nearest tenth of a year. Additional summaries of AE categories of SAEs, AESIs, and study drug related TEAEs by SOC (or AESI category) and PT adjusted for patient-years of exposure will also be generated.

Listings will be provided for all TEAEs, SAEs, TEAEs of special interest, TEAEs leading to study drug discontinuation, and TEAEs leading to death for all patients in the Safety Population. COVID-19-associated AEs will be coded as a specific preferred term in these listings.

A listing of all deaths, including the date of death and primary cause of death, will be presented for all patients in the Safety Population.

3.5.2 Clinical Laboratory Tests

Laboratory panels (hematology, chemistry, and urinalysis, with specific analytes for each panel listed in Protocol Appendix B) will be summarized by scheduled visit, along with changes from baseline to each scheduled post-baseline visit (Protocol Appendix A) for each test. All summary tables will be presented by treatment, for the Safety Population. Descriptive statistics will be provided for continuous variables; for categorical variables, number and percentage will be summarized. Only data from the central laboratory will be summarized. Separate tables will be presented for each laboratory panel. All clinical laboratory results will be displayed in original units as documented in SDTM.

Shift tables (number and percentage) will be provided by CTCAE 5.0 grades from baseline to the worst post-baseline assessment and will be summarized by treatment for selected laboratory tests (hemoglobin, white blood cell count, platelets, liver function tests [alanine aminotransferase, aspartate aminotransferase,, and alkaline phosphatase], and serum creatinine). The worst post-baseline grade (for both directions if applicable) will be derived from all post-baseline visits including scheduled and unscheduled. Additionally, shift tables comparing shift from baseline to each scheduled post-baseline visit with respect to normal ranges (categorizations of low, normal, or high) will be presented for all laboratory parameters where normal ranges are provided.

Additional analysis of laboratory parameters (chemistry and hematology parameters will be summarized separately) will be performed in the Safety Population and will include frequencies for the following post-baseline values:

- Patients with at least a 2-grade increase in CTCAE toxicity grade from baseline in any parameter
- Patients with CTCAE toxicity grade ≥4 in any parameter

Analysis of patients with post-baseline aminotransferase elevations and total bilirubin by category will be performed for the following post-baseline values in the Safety Population and defined as:

- Alanine aminotransferase >3x, >5x, >10x upper limit of normal (ULN)
- Aspartate aminotransferase >3x, >5x, >10x ULN
- Alanine aminotransferase and/or AST >3x, >5x, >10x ULN
- Alanine aminotransferase and AST >3x, >5x, >10x ULN
- Total bilirubin >2x ULN
- Alanine aminotransferase and/or Aspartate aminotransferase >3x ULN, and total bilirubin >2x ULN

A patient with elevated laboratory parameters may belong to more than one category (e.g., if a patient has an Alanine aminotransferase value = 6x ULN, this patient will be presented under both >3x ULN and >5x ULN).

Patients who meet potential Hy's Law laboratory criteria will be listed. Hy's Law laboratory criteria are defined as any elevated Alanine aminotransferase and/or Aspartate aminotransferase of >3x ULN that is associated with both an alkaline phosphatase level <2x ULN and an increase in total bilirubin >2x ULN.

Analysis of patients with post-baseline anemia by category will be performed for post-baseline hemoglobin values in the Safety Population and defined as:

- Baseline value ≥ lower limit of normal (LLN) and postbaseline value <LLN
- Baseline value ≥LLN and postbaseline value <10.0 g/dL
- Baseline value ≥LLN and postbaseline value <10.0 g/dL to 8.0 g/dL
- Baseline value ≥LLN and postbaseline value <8.0 g/dL
- Baseline value ≥10.0 g/dL and postbaseline value <10 g/dL
- Baseline value ≥10.0 g/dL and postbaseline value <10.0 g/dL to 8.0 g/dL
- Baseline value ≥10.0 g/dL and postbaseline value <8.0 g/dL

In the End of Study Analysis for each phase, as summary of recovery in hemoglobin results at the LFU visit by treatment arm will present the number and percentage of patients with a decrease from baseline hemoglobin of ≥1 g/dL at any post-baseline visit while on treatment (i.e. through the EOT visit). Among this subset of patients, the number and percentage of patients with an LFU hemoglobin result meeting the criteria of both an increase of ≥1 g/dL from their lowest on-therapy hemoglobin value and returning to within 1 g/dL below baseline or higher will be presented, both overall and by gender. A corresponding listing of all patients with an on-treatment hemoglobin decline in of 1 g/dL from baseline and their corresponding LFU recovery status will be provided.

All laboratory data will be listed for all patients in the Safety Population, including toxicity grades, normal ranges, and clinically significance flags; values outside their normal range will be flagged as H (high, above normal) or L (low, below normal).

Line plots of mean (+/- SD) for laboratory values (hemoglobin [separate plots for males and female], mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, red blood cell count [separate plots for males and females], reticulocytes percent, hematocrit [separate plots for males and females], white blood cell count, platelets, creatinine clearance, and liver function tests (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) versus visit will also be provided by treatment group. Normal range reference lines will be included on all figures, with the exception of creatinine clearance. Boxplots of change from baseline in hemoglobin [separate plots for males and females], mean corpuscular hemoglobin concentration, mean corpuscular volume, and red blood cell count [separate plots for males and females] will be provided by treatment group.

3.5.3 Vital Signs and Electrocardiograms

Vital signs will be measured at Screening and every scheduled study visit. Vital signs will include temperature, heart rate, blood pressure, and weight.

Summary tables of observed values and changes from baseline to scheduled post-baseline visits will be presented by treatment, for the Safety Population, for each vital sign parameter. Counts and percentages of patients with the following potentially clinically significant abnormal vital signs at any post-baseline visit will be summarized:

- SBP ≥180 mmHg and increase ≥20 mmHg from baseline
- SBP ≤90 mmHg and decrease ≥20 mmHg from baseline or SBP decrease >40 mmHg from baseline
- DBP ≥150 mmHg and increase ≥15 mmHg from baseline
- DBP ≤50 mm Hg and decrease ≥15 mm Hg from baseline
- HR ≥120 bpm and increase ≥15 bpm from baseline
- HR ≤50 bpm and decrease ≥15 bpm from baseline

A 12-lead ECG will be conducted at Screening (in triplicate), Day 1 (Post-treatment) Month 2, Month 4, Month 6, and the EOT Visit (and the Early Termination Visit as applicable). ECG summaries include heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), and QTcF interval (msec).

Summary tables of observed values and changes from baseline to scheduled post-baseline visits will be presented by treatment, for the Safety Population, for each ECG parameter. When ECG data are collected in triplicates (Screening visit only), the average value among three measurements will be summarized.

Electrocardiogram values (the worst interpretation value of the triplicate at Screening) will be summarized by the number and percentage classified as normal, abnormal – not clinically significant, abnormal – clinically significant, or not done at each scheduled visit, by treatment and overall, for the Safety Population.

Counts and percentages of patients with the following potentially clinically significant abnormal QTcF results at any post-baseline visit will be summarized in the Safety Population as follows:

- QTcF >500 msec and baseline ≤500 msec
- QTcF >480 to ≤500 msec and baseline ≤480 msec
- QTcF >450 to ≤480 msec and baseline ≤450 msec
- QTcF change from baseline >30 to ≤60 msec
- QTcF change from baseline >60 msec
- Post-baseline QTcF >500 msec and QTcF change from baseline >30 to ≤60 msec

- Post-baseline QTcF >500 msec and QTcF change from baseline >60 msec
- Post-baseline QTcF >480 to ≤500 msec and QTcF change from baseline >30 to ≤60 msec
- Post-baseline QTcF >480 to ≤500 msec and QTcF change from baseline >60 msec

Listings of vital signs data and ECG data will be presented for all patients in the Safety Population; the listings will state all parameters in their original collection units.

3.5.4 Physical Examinations

A physical examination (PE) of the head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system, and, as appropriate, other body systems will be performed at Screening and at every scheduled study visit.

Abnormal physical examination results at baseline will be recorded as medical history. Post-randomization clinically significant abnormal PE values will be recorded as AEs and summarized and listed as AEs. No specific summaries for the PE values will be created.

3.5.5 Other Safety Assessments

A listing of all pregnancy test results will be provided for all female patients in the Safety Population, where applicable.

3.6 Pharmacokinetic Analysis

Collection times and individual concentrations of epetraborole and the M3 metabolite will be listed individually for all patients treated with epetraborole in the PK Population, but no formal pharmacokinetic analyses will be presented as part of this analysis plan. The results will be incorporated into a population PK analysis described in a standalone Population PK analysis plan.

4 DATA COMMITTEES

4.1 Pharmacokinetic Data Review Committee

Masked individual and composite plasma PK data from an initial group of patients enrolled in the Phase 2 part of the study will be reviewed by a PK Data Review Committee to assess epetraborole exposures. Approximately 40 of the initial patients enrolled may need to be considered in this evaluation to ensure approximately 16 epetraborole-treated patients from the PK Population contribute to the exposure assessment. Review of these PK data will be masked to subject ID and will consist only of an interim PK data review; this will not be a formal review of safety or efficacy. Study enrollment will proceed uninterrupted during this interim PK data assessment.

4.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review specified patient data during the conduct of the study to monitor the safety of patients.

During the conduct of the study, the DSMB will be responsible for periodic review of unblinded safety data by performing a qualitative and quantitative safety assessment. In addition, the DSMB will determine whether the basic study assumptions remain valid, and evaluate whether the overall integrity, scientific merit, and conduct of the study remain acceptable. The DSMB will make recommendations to the Sponsor regarding continuation or termination of the study or suggested changes in the study design/procedures.

Any DSMB decision will be made in the best interest of the safety and well-being of the involved study patients, guided by the principles settled in International Council for Harmonisation Guidelines (ICH) Good

Clinical Practice (GCP) E6, the most recent version of the Declaration of Helsinki, and other relevant local or international regulatory requirements.

Full details of the DSMB will be provided in the EBO-301 DSMB Charter.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

This statistical analysis plan includes following changes from the protocol-specified statistical analyses:

- In secondary efficacy analysis (both Phase 2 and Phase 3), summary of microbiological reinfection and relapse is changed to summarize recurrence only rather than relapse/reinfection at the Month 6 analysis of Phase 2, pending whole genome sequencing;
- In Phase 2 exploratory efficacy analysis, time to $MACrO_2$ response is changed to time to sustained $MACrO_2$ response;
- In Phase 2 exploratory efficacy analysis, time to decrease in colony count category is changed to time to first sustained decrease;
- In Phase 3, the originally specified primary efficacy endpoint in the US (and key secondary endpoint outside the US), clinical response as measured by the $MACrO_2$ PRO, has been replaced with change from baseline to Month 6 in the QOL-B respiratory domain score, and corresponding estimand details for the primary efficacy analysis have been modified accordingly, based on the unblinded results from Phase 2 data;
- In Phase 3 secondary analyses, a new $MACrO_2$ total scaled score has been introduced (Appendix 8.5) for inclusion wherever other PRO continuous score measures (QOL-B, NTM Symptoms Module, and SGRQ-C) are to be analyzed, based on psychometric analysis of pooled Phase 2 data.
- In Phase 3 exploratory efficacy analysis, time to first negative sputum culture through Month 4 and time to decrease in colony count category have been replaced with time to first sustained improvement in QOL-B respiratory domain score by a threshold of 11.1 points and time to first sustained improvement in $MACrO_2$ total scaled score by a threshold of 11.3 points.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

7 REFERENCES

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