CLINICAL STUDY PROTOCOL

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)

NCT05327803

Protocol v5.0 (Amendment 4):
07 June 2023

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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 ($MACrO_2$)

Investigational Product: Epetraborole tablets

Protocol Number: EBO-301

Universal Trial Number (UTN): U1111-1278-5148

Sponsor:

AN2 Therapeutics, Inc.
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Menlo Park, CA 94027 United States
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Protocol Version		Date
1.0	Original	30 December 2021
2.0	Amendment 1	22 March 2022
3.0	Amendment 2	29 June 2022
4.0	Amendment 3	08 February 2023
5.0	Amendment 4	07 June 2023

SPONSOR SIGNATURE PAGE

STUDY TITLE: 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 ($MACrO_2$)

As the AN2 Therapeutics, Inc. ("Sponsor") representative, I confirm that the study Protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the Investigational Product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), the International Council for Harmonization guidelines on Good Clinical Practice, and all applicable local or regional regulations.

Signature and Date (DDMMMYYYY)

[redacted]

[redacted]
AN2 Therapeutics, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this Protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this Protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this Protocol and access to all information furnished by AN2 Therapeutics, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to AN2 Therapeutics, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by AN2 Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct the study in compliance with this Protocol, and in full accordance with Institutional Review Board/Ethic Committee Regulations, International Council for Harmonisation Guidelines for Good Clinical Practices, and all applicable local or regional regulations.

_____

Investigator's Signature and Date (DDMMMYYYY)

_____

Investigator's Printed Name

SYNOPSIS

TITLE: 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 ($MACrO_2$)

PROTOCOL NUMBER: EBO-301

INVESTIGATIONAL PRODUCT: Epetraborole tablets

PHASE: 2/3

INDICATION: Treatment-refractory *Mycobacterium avium* complex (MAC) lung disease

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 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], 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 radiographic 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, and 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 radiographic 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

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 conversion monthly through Month 6 in the Micro-ITT Population. Sputum 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 conversion monthly through Month 6 in the Micro-ITT Population. Sputum 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, QOLB, 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 pathogen[s] different from the baseline MAC isolate) and relapse (pulmonary MAC infection caused by the same baseline MAC isolate) at Month 6, End of Therapy (EOT), and Late Follow-up (LFU) in the Micro-ITT Population
- Characterization of epetraborole plasma exposure in a 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 Population
- PRO symptom/function-based clinical response using mean changes in PRO domain scores (eg, QOLB, 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

INCLUSION AND EXCLUSION CRITERIA:

The eligibility criteria are the same for both the Phase 2 and Phase 3 parts of the study.

Inclusion Criteria:

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients who are 18 years of age or older.
2. Willing and able to provide written informed consent.
3. Patients with a diagnosis of treatment-refractory MAC lung disease, defined as respiratory specimen positive for MAC despite receiving a combination regimen of ≥2 antimycobacterial agents administered for ≥6 months, meeting all of the following (a) Microbiological, (b) Clinical, (c) Radiographic, and (d) OBR criteria:

a. *Microbiological criteria*:
   - **Documentation of at least 1 *Pre-Study* MAC-positive respiratory specimen** (sputum or deep bronchial specimen) collected per standard of care within 6 months prior to signing the informed consent form (ICF); see Section 7.5.3.1 for details.
   - **At least 1 *Screening* MAC-positive expectorated or induced sputum sample**. See Section 7.5.3.2 for details, including enrollment of selected patients with a *pending* Screening culture result.

b. *Clinical criteria*: At least 2 of the following patient-reported clinical symptoms, the "key" symptom of which must be of moderate or greater severity, ongoing at the time of randomization, according to the MACrO$_2$ PRO instrument (see Section 7.5.5.1):
   - Cough with sputum production
   - Cough without sputum (dry cough)
   - Chest congestion
   - Hemoptysis
   - Dyspnea (shortness of breath)
   - Fatigue
   - Night sweats or unusual sweating

c. *Radiographic criteria*: Non-contrast chest CT scan within 6 months prior to signing the ICF (*Pre-Study* chest CT) or within the Screening Period (*Screening* chest CT) with abnormalities consistent with MAC lung disease based on local interpretation (eg, Investigator or local radiologist). See Section 7.5.1.4 for details, including allowable types of chest CTs.

d. *OBR criteria:* An OBR is a combination regimen that consists of ≥2 antimycobacterial agents. The patient-specific OBR must be administered for a minimum duration of 6 consecutive months that is either ongoing at the time of Screening or was stopped or paused no more than 12 months before Screening (exceptions to treatment with OBR for 6 consecutive months may include changes to dose level or frequency during therapy, replacement of a component of the background regimen with a member of the same drug class, and/or short [eg, approximately 6 weeks, cumulatively] interruptions of therapy).

   Patients whose OBR was stopped prior to Screening must have a documented prior MAC-positive respiratory specimen despite receiving a combination regimen of ≥2 antimycobacterial agents for ≥6 months. At Screening, these patients must be restarted on an OBR consisting of ≥2 agents from their most recent regimen. The OBR regimen administered during Screening must be continued after randomization. See details in Section 5.7.1.

4. Patients who are willing to comply with all the study activities and procedures throughout the duration of the study, including willingness to continue OBR (ie, combination antimycobacterial treatment regimen including inhaled and parenteral medications, as appropriate, in addition to oral medications) and comply with all planned study visits and study procedures (including all planned sputum collections) from

Screening through the LFU Visit (duration of study participation up to approximately 19 months, not including Screening).

5. Patients must agree to use an effective method of birth control, if applicable, as follows:
    a. Females of childbearing potential (FOCPs) must commit to either sexual abstinence or use of at least 2 medically accepted, effective methods of birth control, which can be comprised of a combination of a highly effective method (eg, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections or locally approved method[s]; for example, of these, only oral contraceptive and indwelling intrauterine device are acceptable in Japan) and a barrier method (eg, condom or locally approved method[s]) from Screening through the EOT Visit and for 90 days following the last dose of study drug. Nonchildbearing potential is defined as postmenopausal (ie, amenorrheic for at least 1 year) or surgically/naturally sterile.
    b. Male patients who are sexually active with a FOCP must agree to use an effective barrier method (ie, locally approved method[s]) of contraception from Screening through the EOT Visit and for 90 days following the last dose of study drug.
6. Patients expected to survive with continued antimycobacterial therapy and appropriate supportive care from Screening through the LFU Visit, in the judgment of the Investigator.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from participation in both the Phase 2 and Phase 3 parts of the study:

1. Patients with a presence of any suspected or confirmed disease or condition at Screening or the time of randomization that, in the opinion of the Investigator, may confound the assessment of symptom-based clinical response, including, but not limited to, the following:
    - Radiographic presence of any cavity >5.0 cm internal diameter (see Section 7.5.1.4)
    - Cystic fibrosis or other inherited disorders of airway ciliary dysfunction (eg, primary ciliary dyskinesia)
    - Active allergic bronchopulmonary mycosis
    - Anticipated or planned lung surgery for treatment of MAC lung disease
    - Disseminated MAC infection, or other known or suspected non-pulmonary source of infection (eg, infective endocarditis, osteomyelitis, meningitis, or urinary tract infection) requiring non-study antimicrobial therapy
    - Concomitant pulmonary infection requiring antimicrobial therapy including infection caused by fungi, viruses, non-MAC mycobacteria (eg, *Mycobacterium tuberculosis*, *Mycobacterium abscessus*, *Mycobacterium kansasii*), or other bacteria (eg, *Pseudomonas aeruginosa*, *Staphylococcus aureus*).

      Patients with MAC lung disease and concomitant non-MAC lung infection *requiring antimicrobial therapy* must complete the antimicrobial treatment prior to randomization. Patients with respiratory specimen cultures that contain growth of non-MAC organisms that are deemed by the Investigator to be respiratory tract

colonizers and *who do not require or receive specific antimicrobial therapy* may remain eligible. The Investigator should discuss such cases with the Medical Monitor prior to randomization and provide rationale for study eligibility in the source document.

2. Patients with active pulmonary malignancy (primary or metastatic) or any malignancy that required or would require chemotherapy or radiation therapy within 1 year prior to randomization through the LFU Visit.
3. Patients with creatinine clearance (CrCl) of <30 mL/min, as estimated by the Cockcroft-Gault formula, at Screening:

   Estimated CrCl (mL/min) = (140 – Age [years]) × Actual Body Weight [kg] × [0.85 if Female]) / (72 × Serum Creatinine [mg/dL])
4. Patients with hemoglobin <10.0 g/dL or <6.2 mmol/L (Grade 2 anemia or worse, based on Common Terminology Criteria for Adverse Events [CTCAE; NIH, 2017]) at Screening; donation of blood or plasma within 28 days prior to randomization; or symptomatic loss of blood or hemorrhage within 28 days prior to randomization. Patients with an initial Screening hemoglobin of ≥10.0 g/dL to < lower limit of normal (LLN) or ≥6.2 mmol/L to <LLN will be retested at the central clinical laboratory to confirm eligibility and results must be available prior to randomization.
5. Patients with severe hemoptysis within 28 days prior to randomization, defined as >100 mL (approximately >7 tbsp blood) over any 24-hour period or severe or extremely severe hemoptysis based on the $MACrO_2$ PRO at baseline.
6. Patients with severe hepatic impairment, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) or total bilirubin >2 × ULN, or clinical signs of cirrhosis or end-stage hepatic disease (eg, ascites, hepatic encephalopathy).
7. Patients who are pregnant or breastfeeding.
8. Patients with a mean QT interval corrected using Fridericia's formula (QTcF) >480 msec based on triplicate 12-lead ECGs at Screening.
9. Patients with an immunodeficiency or an immunocompromised condition and risk for an opportunistic pulmonary infection, including:
   - Known history of human immunodeficiency virus (HIV) infection *plus* either an active acquired immunodeficiency syndrome (AIDS) defining illness in the past 12 months, or a known cluster of differentiation 4 (CD4) count <200/mm^3 within the past 12 months
   - Neutropenia at Screening (absolute neutrophil count <1,000 neutrophils/mm^3)
   - Use of immunosuppressive therapy at Screening that in the opinion of the Investigator may place the patient at risk for an opportunistic pulmonary infection, including transplant rejection medication and chronic systemic corticosteroids defined as ≥20 mg/day of prednisone or systemic equivalent for >4 weeks.

10. Patients with an anticipated start of new non-study antimycobacterial therapy to be administered at any time between Screening and EOT.
11. Patients who have participated in a clinical trial of an investigational agent within 30 days (or 5 half-lives, whichever is longer) prior to Screening.
12. Patients with any prior exposure to epetraborole.
13. Patients with any condition that, in the opinion of the Investigator, interferes with the ability to safely complete the study or adhere to study requirements, including the patient's inability or unwillingness to comply with all study assessments and visits.
14. Patients with a hypersensitivity to any epetraborole excipient (ie, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc).

For eligibility purposes, vital signs, clinical laboratory tests, and ECGs may be repeated once if an abnormal result is observed at the initial reading during Screening.

STUDY DESIGN:

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.

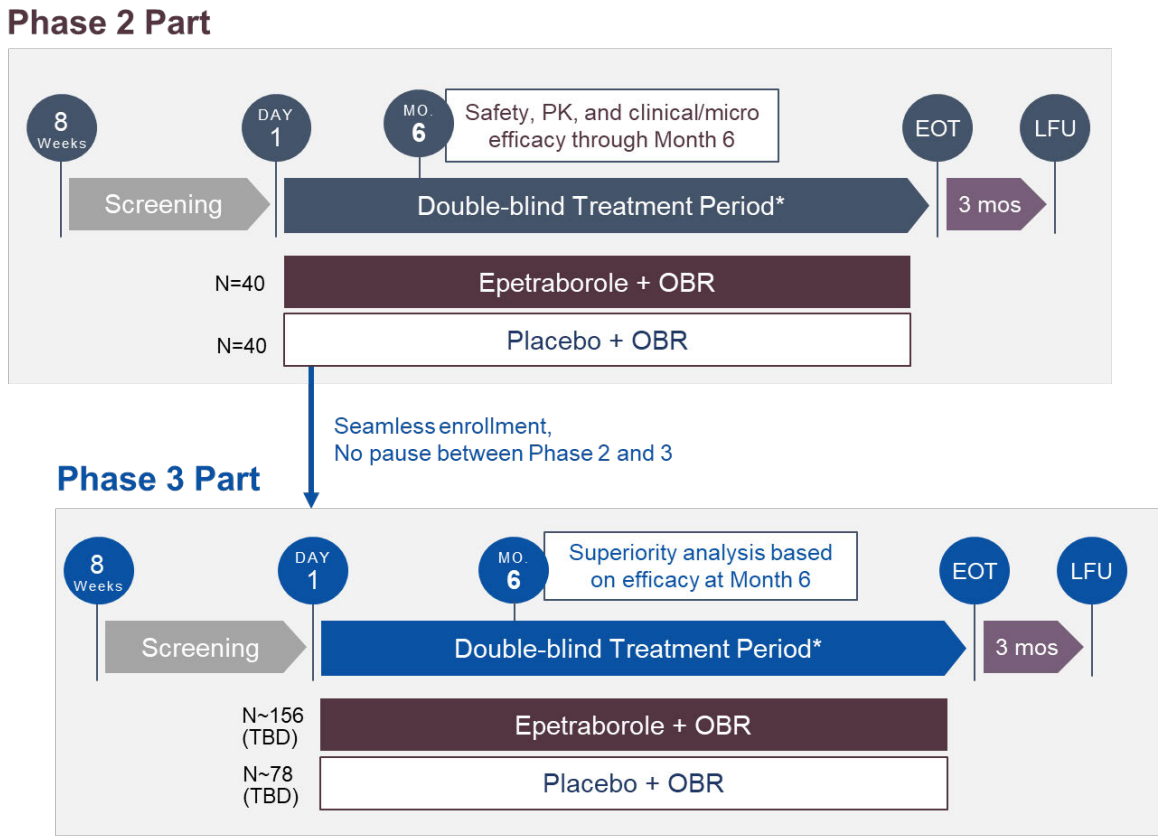
This study features a sequential Phase 2/3 approach with an initial Phase 2 assessment of symptom-based clinical responses, microbiological responses, safety, and PK associated with oral epetraborole, prior to the superiority analysis of oral epetraborole versus placebo in the Phase 3 part of the study. Results from the Phase 2 part of the study will inform the specific PRO and the symptom-based clinical response definition and inform sample size re-estimations to be used in the Phase 3 part of the study. In addition, a PK analysis from an initial group treated with epetraborole in the Phase 2 part of the study will assess oral epetraborole exposures in patients with treatment-refractory MAC lung disease.

In the Phase 2 part of the study, approximately 80 patients will be randomized in a 1:1 ratio (40 patients receiving active epetraborole tablets and 40 patients receiving matching placebo tablets) using an Interactive Responsive Technology (IRT) system and stratified by baseline use of ALIS and age at informed consent (<65 years versus ≥65 years). The Phase 2 part of the study includes a blinded psychometric analysis to assess the psychometric properties (ie, reliability, validity, ability to detect change [responsiveness], and clinically meaningful within-patient changes in scores) of a novel "$MACrO_2$ PRO" instrument. In addition, symptom-based clinical responses will be assessed using blinded data, to inform the measurement of clinical response in the Phase 3 part of the study. The Phase 2 psychometric data analyses will support selection and positioning of PRO measures as endpoints for Phase 3. Decisions will be based on item-level or domain-level (when appropriate) performance and ability to detect change (responsiveness) in Phase 2. Up to 40 eligible patients in the Phase 2 part of the study will participate in an optional qualitative embedded interview. Interviews will qualitatively evaluate the proposed symptom-based clinical response definition within the context of the clinical study. 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.

After the last patient in Phase 2 completes the Month 6+1 week PRO assessment, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for Phase 2 data analyses, but study staff conducting psychometric validation analyses will remain blinded. Patients, Investigators, and other study staff 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 clinical symptom responses, microbiological, safety, and PK data collected at multiple time points through Month 6. Patients enrolled in the Phase 2 part of the study will not be eligible for participation in Phase 3.

Figure S1 presents the study design.

Figure S1. Study Design



* Patients who culture convert will be treated for 12 months from 1st negative culture per treatment guidelines.
EOT = End-of-Therapy; LFU = Late Follow-up; OBR = Optimized Background Regimen; TBD = Final sample size to be confirmed based on Phase 2 Part data

The Phase 3 part of the study will test the superiority of epetraborole + OBR compared to placebo + OBR. In this part of the study, approximately 234 patients are planned to be randomized in a 2:1 ratio (156 patients receiving active epetraborole tablets and 78 patients receiving matching placebo tablets) using an IRT system and stratified by baseline use of ALIS and presence or absence of any fibrocavitary disease. The current symptom-based clinical response definition (using the $MACrO_2$ PRO) in Phase 3 is a placeholder to be verified after Phase 2 analyses, which will be based on data through Month 6. In addition, the Sponsor will determine if the sample size for Phase 3 should be adjusted and will confirm the Phase 3 epetraborole dosage regimen based on the observed plasma epetraborole exposure. Such changes will be addressed in a protocol amendment as appropriate. After the last patient in Phase 3

completes the Month 6 Visit, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for Phase 3 data analyses; patients, Investigators, and other study staff 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, microbiological, safety, and PK data collected at multiple time points through Month 6.

All patients in the study will receive a minimum of 6 months of blinded study drug treatment. At the Month 6 Visit, all available sputum culture results will be assessed by the Investigator to determine whether a patient is a converter or non-converter. Patients who are assessed as converters will continue taking blinded study drug for 12 months after the first month that defines sputum culture conversion, up to a maximum of 16 months. Patients who are assessed as non-converters will discontinue study drug at the Month 6 Visit. See additional details in Section 3.1.1.

During the conduct of the study, an independent Data and Safety Monitoring Board (DSMB) will be responsible for periodic review of unblinded study 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. Additional details are available in the EBO-301 DSMB Charter.

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 randomized patients (40 patients in the epetraborole + OBR group and 40 patients in the placebo + OBR group).
- The Phase 3 part of the study will consist of approximately 234 randomized patients (156 patients in the epetraborole + OBR group and 78 patients in the placebo + OBR group). The number of patients in the Phase 3 part of the study may be adjusted based on the results of Phase 2 analyses.

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 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 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

SITES:

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

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 (2 oral tablets QD)

CLINICAL ASSESSMENTS USING PATIENT-REPORTED OUTCOME MEASURES:

In both the Phase 2 and Phase 3 parts of the study, each patient will complete the same set of PRO measures including $MACrO_2$, QOL-B, NTM Symptoms Module, SGRQ-C, and global assessment scales (Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change [PGIC]). In addition, Investigators will complete the Clinician Global Impression of Severity (CGIS) and Clinician Global Impression of Change (CGIC). An electronic PRO system will be used during the study to allow patients to complete the study questionnaires electronically. PROs will be completed at the time points listed in the Schedule of Assessments. Select PROs will be completed twice before the first dose of study drug to assess test-retest reliability. The $MACrO_2$ and PGIS will be completed at additional time points to further assess test-retest reliability. PRO test-retest reliability will be assessed in Phase 2 and may be analyzed in Phase 3 if deemed necessary.

The $MACrO_2$ PRO will be psychometrically evaluated in a blinded manner in the Phase 2 part of the study and a formal psychometric analysis plan will be developed. The planned analyses will include item level performance (distribution of responses, missing data, and floor and ceiling effects); construct validity (including known-groups and concurrent validity); test-retest reliability; sensitivity to change; and defining meaningful change thresholds (ie, using global anchor items and clinical outcomes to define response). The $MACrO_2$ PRO measure may be further refined following the psychometric analyses. The selection of the final PRO measure to use as the primary endpoint (in the US) or key secondary endpoint (outside the US) in the Phase 3 portion of the study and the timing of this assessment will be based on the $MACrO_2$ PRO item performance and sensitivity to change by treatment outcomes.

QUALITATIVE EMBEDDED INTERVIEW ASSESSMENTS:

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. All interviews will be conducted via telephone or web-based teleconference, based on participant preference and capabilities. Interviewers will use an open-ended, semi-structured interview guide to lead the discussion. Interviews will be conducted in English or other approved language, will last approximately 30 to 45 minutes, and will be audio-recorded. The interview will be conducted within 2 weeks (up to 4 weeks maximum) after the Month 6 Visit or within 1 week (up to 3 weeks maximum) after the EOT Visit (if EOT occurs within first 6 months and if the patient has completed at least 8 weeks of treatment). Interviews will qualitatively evaluate the proposed symptom-based clinical response definition within the context of the clinical study.

MICROBIOLOGICAL ASSESSMENTS:

Appropriate respiratory specimens are required during the Screening and Treatment Periods; 2 to 3 sputum samples will be collected at each time point outlined in Appendix A and may be collected on the same day or within a 5-day window beginning with collection of the first sample. If at least 1 of the sputum samples is MAC positive, the patient will be considered

positive for MAC at that time point. For example, a single MAC-positive *Screening* sputum sample is sufficient to meet the microbiological requirement for enrollment. Induced or expectorated sputum samples are required at all time points, except the *Pre-Study* respiratory specimen may be either an induced or expectorated sputum sample or a deep bronchial specimen (see Inclusion Criterion 3.a). If a patient is clinically improving and no longer coughing or producing sputum, every effort should be made to collect sputum samples using sputum induction techniques. If a sputum sample could not be collected despite reasonable efforts (eg, due to a non-productive cough or resolution of cough), the reason(s) the sputum sample was not collected should be documented in the source records. Patients with missing sputum samples should not be prematurely discontinued from study drug or withdrawn from the study. The Investigator should discuss such cases with the Medical Monitor.

Sputum samples collected during the Screening Period and at designated time points during the study will be sent to the regional or central microbiological laboratory for mycobacterial culture, identification, and quantification. Susceptibility and molecular testing (if applicable) of isolates are performed by the central microbiology laboratory.

The 8-week Screening Period allows for culture and identification of MAC isolates. Susceptibility and molecular testing (if applicable) results are not required prior to randomization.

Microbiological evaluation of sputum samples will include improvement in quantitative colony counts. Quantification of bacteria via colony counts on solid agar will be performed and assigned a categorical score. An improvement in quantitative culture counts will be defined as a reduction in ≥1 categorical score from the previous month's categorical culture score.

Molecular testing, including whole genome sequencing, may be performed to determine genetic relatedness of select baseline/postbaseline isolates.

Additional details, including instructions for collecting, processing, and shipping sputum specimens, will be provided in the Laboratory Manual.

RADIOGRAPHIC ASSESSMENTS:

Study chest CT scans will be evaluated to assess eligibility and pulmonary radiographic response during the study. All chest CTs must be non-contrast and consist of contiguous sections through the lungs, each section of ≤3 mm thickness. Low-dose CT scans are acceptable. The interpretation of *Screening* chest CTs (to assess for abnormalities consistent with MAC lung disease, per Inclusion Criterion 3.c) will be performed locally by the site (eg, Investigator or local radiologist). Post-Screening, digital images of chest CTs will be evaluated and interpreted at a central site by a member of an independent team of blinded radiologists. Radiographic response will be evaluated based on severity, extent of pulmonary disease, and overall improvement between baseline (*Screening* CT scan) and Month 6 and between baseline and EOT.

PHARMACOKINETIC ASSESSMENTS:

Blood samples for PK analyses will be collected from all patients in a blinded manner after administration of study drug in a fasted state. A population PK analysis will be performed to assess exposure and PK parameters of epetraborole.

SAFETY ASSESSMENTS:

Assessments of safety will include the following:

- Vital signs
- Laboratory tests (including chemistry, hematology, and urinalysis)
- 12-lead ECG parameters
- Adverse events (AEs)

Treatment-emergent adverse events (TEAEs) will be collected from the time of the first dose of study drug through EOT. All serious AEs (SAEs) occurring from the time of informed consent through LFU will be collected.

STATISTICAL ANALYSES:

Analysis Populations:

The following analysis populations will be defined in this study:

- Intent-to-Treat (ITT) Population: All patients who were randomized, regardless of whether they received any study drug
- Safety Population: Randomized patients who received any amount of study drug
- Micro-ITT Population: Patients who meet the definition for the ITT Population and have MAC culture-positive *Pre-Study* and *Screening* respiratory specimens (per Inclusion Criterion 3.a). Primary efficacy endpoint analyses in both Phase 2 and Phase 3 parts of the study will be performed in this patient population.
- Per-Protocol Population: Patients who meet the definition for the ITT Population and have no important protocol deviations that would affect the assessment of the primary efficacy outcome
- PK Population: All patients treated with at least 1 dose of epetraborole and who have at least 1 analyzable PK sample
- 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), Day 1, and at least Month 3 and/or Month 6 (for all other calculations).
- Embedded Interview Population (applicable to Phase 2 part only): Up to 40 Phase 2 patients who meet Micro-ITT Population and interview eligibility criteria (per Section 7.5.6)

Efficacy:

Phase 2 Part of the Study

The Phase 2 part of the study will assess the performance of the $MACrO_2$ PRO, including responsiveness to change, with the aim of informing selection of the optimal PRO to be used in the Phase 3 part of the study. Psychometric analyses will aim to identify the most appropriate threshold to use within the target population for the individual $MACrO_2$ PRO items. This process will be outlined in the psychometric analysis plan. In summary, anchor-based approaches will be used to assess and confirm the proposed definition of clinical response (ie,

improvement of ≥1 grade in the key symptom with no worsening of other symptoms for the $MACrO_2$ PRO). Empirical cumulative distribution function and probability density plots will also be examined. Distribution-based analyses will be used as supplemental evidence. Anchors will include other PRO measures (ie, the PGIS and PGIC) or clinical outcomes such as microbiological response. The results will be triangulated with the anchor-based analyses considered to be the primary evidence, distribution-based analyses treated as secondary evidence, and results from the embedded interviews to determine a single responder definition threshold or narrow ranges of values for the $MACrO_2$ PRO items.

In addition to the evaluation of the PROs, endpoints from the Phase 2 part of the study will undergo statistical analyses to estimate the effect of randomized treatment. The number and percentage of PRO symptom/function-based clinical responders and clinical non-responders will be presented by treatment group, as will the percentage of patients achieving a microbiological improvement or a microbiological sputum culture conversion. In each case, the response rate will be compared between treatment groups using the method of Miettinen and Nurminen. Statistical analysis of all endpoints for the Phase 2 part of the study will be described in the statistical analysis plan(s) (SAP[s]).

After the last patient in Phase 2 completes the Month 6+1 week PRO assessment, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for Phase 2 data analyses, but study staff conducting psychometric validation analyses will remain blinded. Patients, Investigators, and other study staff will also remain blinded to treatment assignment through LFU (see Study Blinding Plan). Prespecified members of the Sponsor and non-Sponsor analysis teams will review unblinded results from the Phase 2 analyses, based on data through Month 6, to verify the appropriate PRO measure and clinical response determinations for the superiority analysis in the Phase 3 part of the study. The current symptom-based clinical response definition (using the $MACrO_2$ PRO) in Phase 3 is a placeholder to be verified after Phase 2 analyses. Potential changes to clinical response criteria in the Phase 3 part of the study will be programmatical in nature and will not affect study conduct; regardless of the PRO or clinical responses determined for the Phase 3 primary analysis, patients in both the Phase 2 and Phase 3 parts of the study will complete the same set of PRO measures and microbiological assessments according to the Schedule of Assessments.

Phase 3 Part of the Study

The number and percentage of PRO symptom/function-based clinical responders and clinical non-responders will be presented by treatment group. Patients with missing data or incomplete PRO data at each relevant time point will be considered an indeterminate response and will be analyzed as a clinical non-responder. The clinical response rate will be compared between treatment groups using the method of Miettinen and Nurminen. Analyses of PRO symptom/function-based clinical responses will be conducted in the Micro-ITT and Per-Protocol populations.

The number and percentage of patients with microbiological responses by both decrease in MAC colony counts of ≥1 category and sputum culture conversion will be presented by treatment group. Microbiological responses will be compared between treatment groups using the method of Miettinen and Nurminen. Analyses of microbiological responses will be conducted in the Micro-ITT Population.

As there is 1 primary endpoint and 1 key secondary endpoint in each region (in the US or outside the US), a hierarchical testing approach will be applied, whereby the primary endpoint will be

tested, and if superiority is concluded for the primary endpoint, the key secondary endpoint will then be tested. Note that, although the ordering of the primary endpoint and key secondary endpoint is reversed for the US and outside the US, the same approach to hierarchical testing will be used for the primary and key secondary endpoint appropriate for that region. As no specific claims are intended for other secondary endpoints, no further multiplicity testing will be applied for the other secondary and exploratory endpoints.

Analyses of the exploratory efficacy outcomes will be conducted to support the findings of the primary and secondary efficacy outcomes and will be described in the SAP(s).

Safety:

Safety will be evaluated for the Safety Population by presenting the summaries of TEAEs, clinical laboratory evaluations (chemistry, hematology, and urinalysis), vital signs, and 12-lead ECG parameters.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v25.0 or later. An overall summary of AEs will be provided by treatment group. The incidence of TEAEs will be presented by SOC and PT; by SOC, PT, and relationship to study drug; and by SOC, PT, and maximum severity. SAEs and TEAEs that lead to premature discontinuation of study drug will also be presented by SOC and PT.

Descriptive statistics for clinical laboratory results, vital signs, and 12-lead ECG parameters, including change from baseline, will be presented by time point collected. Incidences of potentially clinically significant clinical laboratory results, vital signs, and 12-lead ECG parameters, as defined in the SAP(s), will also be summarized.

The independent DSMB will periodically review unblinded safety data, including vital signs, ECG findings, laboratory tests (eg, hematology, blood chemistry), AEs (including SAEs and adverse events of special interest [AESIs]), and any other relevant safety information, to perform a qualitative and quantitative safety assessment during both Phase 2 and Phase 3 parts of the study (see EBO-301 DSMB Charter).

Pharmacokinetics:

Plasma PK will be analyzed for all patients treated with at least 1 dose of epetraborole and who have at least 1 analyzable PK sample. Plasma PK samples obtained from the epetraborole group will be analyzed using a validated assay by a central bioanalytical laboratory. Samples from placebo-treated patients will not be analyzed. 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 in approximately 16 epetraborole-treated patients from the PK Population. Review of these PK data will be blinded 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. The methods to be employed for this interim analysis will be presented in a data analysis plan and results reported in a separate PK report.

SAMPLE SIZE DETERMINATION:

Phase 2 Part of the Study:

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 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 correlation coefficient of 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 5 response options). In addition, using assumed true response rates of 30% for the epetraborole arm and 10% for the placebo arm for either a PRO symptom-based clinical response (in the US) or a microbiological culture conversion response (outside the US), a Phase 2 evaluation in 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 Part of the Study:

No data are available on clinical symptom 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 revealed Month 6 sputum culture conversion rates of 29.0% compared with 8.9%, respectively. 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 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 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 epetraborole and 78 placebo patients) 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); 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 through Month 6. Any needed sample size adjustment for Phase 3 will be determined as part of the review of unblinded Phase 2 data.

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Abbreviation	Definition
ADH	alcohol dehydrogenase
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALIS	amikacin liposome inhalation suspension
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
CD4	cluster of differentiation 4
CDAD	*Clostridioides difficile*-associated diarrhea
C. difficile	*Clostridioides difficile*
CFR	Code of Federal Regulations
CGIC	Clinician Global Impression of Change
CGIS	Clinician Global Impression of Severity
CLSI	Clinical and Laboratory Standards Institute
COPD	chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOT	End of Therapy
ERS	European Respiratory Society
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
FAS-PRO	Full Analysis Set-Patient-Reported Outcome
FDA	Food and Drug Administration
FOCP	female of childbearing potential
GCP	Good Clinical Practice
GI	Gastrointestinal
HFM	hollow-fiber macrophage
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IMP	investigational medicinal product

Abbreviation	Definition
IR	immediate-release
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
LFU	Late Follow-up
log	Logarithmic
LPA	line probe assay
LLN	lower limit of normal
MAC	*Mycobacterium avium* complex
MALDI-TOF	matrix-assisted laser desorption ionization-time of flight
M. avium	*Mycobacterium avium*
M. chimaera	*Mycobacterium chimaera*
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
Micro-ITT	Microbiological Intent-to-Treat
M. intracellulare	*Mycobacterium intracellulare*
NADPH	nicotinamide adenine dinucleotide phosphate
NIMP	non-investigational medicinal product
NTM	nontuberculous mycobacteria(l)
OBR	optimized background regimen
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	preferred term
QD	once daily
QOL-B	Quality of Life-Bronchiectasis
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
rRNA	ribosomal ribonucleic acid
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
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to reach the maximum concentration
tRNA	transfer ribonucleic acid
ULN	upper limit of normal

1. INTRODUCTION AND BACKGROUND INFORMATION

Oral epetraborole tablets are being developed for the treatment of serious infections for which there is a high unmet need for new antimicrobial therapy in combination regimens, such as mycobacterial disease (eg, drug-resistant nontuberculous mycobacteria [NTM] disease and tuberculosis). The current indication under investigation is treatment-refractory *Mycobacterium avium* complex (MAC) lung disease; treatment refractory lung disease is defined as respiratory specimen positive for MAC despite receiving a combination regimen of ≥2 antimycobacterial agents administered for ≥6 months.

1.1. Background

NTM are a phenotypically-diverse group of species and subspecies found throughout the environment. Lung disease is the most common manifestation of human NTM infection. MAC, consisting of *Mycobacterium avium (M. avium)*, *M. intracellulare*, and *M. chimaera,* is the most frequent cause of NTM lung disease (Lande, 2018; Johansen, 2020). Multiple host factors, such as increasing age of the global population, structural lung disease, and immunosuppression have contributed to a rise in the global incidence of NTM lung disease, which frequently exceeds the global incidence of new tuberculosis cases in developed countries (Johansen, 2020).

NTM lung disease is a chronic and debilitating disease that causes significant morbidity and mortality, and negatively impacts a patient's quality of life. The clinical manifestations and symptoms caused by NTM lung disease are highly variable among patients (eg, cough with sputum production, cough without sputum [dry cough], chest congestion, hemoptysis, dyspnea [shortness of breath], fatigue, night sweats or unusual sweating) and clinical disease presentation is strongly dependent on a patient's underlying lung disease and comorbid conditions (Larsson, 2017). NTM lung disease is most associated with 2 distinct radiographic patterns: nodular bronchiectasis and fibrocavitary lung disease (Kwon, 2016). Nodular bronchiectatic disease is the most common form of NTM lung disease, predominantly affecting the mid or lower lung zones; it features multifocal bronchiectasis with peripheral nodules (Larsson, 2017; Daley, 2020) and is typically caused by MAC species. It tends to occur in middle-aged or older nonsmoking women with lean body habitus (Weiss, 2012). Progression of nodular bronchiectatic NTM lung disease can be very slow, occurring over months or years (Weiss, 2012). In contrast, fibrocavitary NTM lung disease features tuberculosis-like cavitary lesions, predominantly in the upper lobes (Larsson, 2017), and is associated with relatively rapid disease progression. It frequently develops in older men with a history of smoking and underlying lung disease (eg, chronic obstructive pulmonary disease, previous tuberculosis). However, it must be emphasized that overlap of symptoms and radiographic findings between these 2 forms of NTM lung disease is not uncommon (Koh, 2017).

The primary therapeutic intervention to treat proven NTM lung disease is antibiotic treatment to eliminate the causative pathogen, and thereby to prevent progression of NTM-associated lung destruction and respiratory failure (Daley, 2020). Current American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) treatment guidelines for NTM lung disease utilize complex treatment regimens of long duration. Guideline-recommended treatments for treatment-naïve MAC lung disease include a 3-drug regimen administered for a duration of approximately 1.5 years. No standard treatment regimen exists for

treatment-refractory MAC lung disease (Daley, 2020; Haworth, 2017). Patient-centered NTM treatment priorities include the need for improved efficacy (measured by sputum culture conversion) that leads to reducing treatment burden, including a reduction in the duration of treatment; identifying new active drugs with fewer side effects; and eliminating the need for intravenous (IV) administration of drugs (Henkle, 2016).

Epetraborole oral tablets would extend the armamentarium of treatment options available to physicians and offer the potential to decrease the need for potentially toxic or unproven therapies. Epetraborole binds to and inhibits the bacterial leucyl-tRNA synthetase, thereby disrupting protein synthesis and blocking the editing function of this critical bacterial enzyme. A number of in vitro and in vivo studies were conducted to evaluate the antibacterial potential of epetraborole against a variety of mycobacterial species including *M. avium*, *M. intracellulare*, and *M. chimera* (see current Investigator's Brochure).

1.1.1. Epetraborole Nonclinical Primary Pharmacodynamics

1.1.1.1. In vitro

The epetraborole minimum inhibitory concentration (MIC) values for 51 isolates of MAC ranged from 0.25 to 8 µg/mL as determined using Clinical and Laboratory Standards Institute (CLSI) MIC testing methodology (CLSI M24-2018). The epetraborole modal MIC, MIC_{50} and MIC_{90} were 2, 2, and 8 µg/mL, respectively. In addition, 3 clarithromycin-resistant MAC isolates had epetraborole MIC values of 0.5 to 2 µg/mL, and 9 amikacin-resistant isolates had epetraborole MIC values of 0.5 to 8 µg/mL, suggesting that clarithromycin and amikacin resistance do not affect epetraborole in vitro activity.

In an in vitro selectivity screen with 55 off-target receptors, enzymes, and ion channels, epetraborole showed no significant activity (IC_{50} >10 µM). In vitro studies with epetraborole in combination with clarithromycin, rifabutin, ethambutol, amikacin, and bedaquiline demonstrated that there are no antagonistic interactions with epetraborole in any combination on in vitro activity against NTM isolates.

1.1.1.2. In vivo

In vivo activity of epetraborole monotherapy and combination therapy has been investigated using a mouse model of chronic MAC lung infection using MAC isolates with epetraborole MIC values ranging from 2 to 8 µg/mL. In the mouse chronic model, infection is allowed to proceed for 28 days before the initiation of 56 days of therapy. Epetraborole demonstrated dose-dependent efficacy in this model with respect to reduction in bacterial burden in the lung. Against *M. avium* 2285, >2-logarithmic $(log)_{10}$ kill was observed with a dose of epetraborole >1 mg/kg/day orally, and the extent of bacterial kill was greater than that observed with 250 mg/kg/day clarithromycin. Against 4 additional MAC isolates, epetraborole administered orally at 100 to 300 mg/kg QD and 400 mg/kg administered every other day caused 2- to 4.8-log_{10} reduction in lung bacterial burden compared to the Day 28 controls. Furthermore, when 200 mg/kg epetraborole QD was combined with the standard of care regimen (clarithromycin 250 mg/kg, ethambutol 100 mg/kg, and rifabutin 100 mg/kg dosed orally QD), efficacy was significantly improved against all isolates compared to standard of care regimen alone, with reduction in viable bacteria in the lung ranging from 4.6 to 5.6 log_{10}. The area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24}) associated with the

200 mg/kg dose in a satellite pharmacokinetic (PK) study was 16.7 µg·h/mL, which is within the range of the AUC_{0-24} values observed with the 500 mg QD oral dose in humans, as measured in healthy volunteers in Study EBO-101.

1.1.2. Epetraborole Nonclinical Experience

The results from nonclinical secondary pharmacodynamics, safety pharmacology, pharmacokinetics and product metabolism, and toxicology studies are provided in the current Investigator's Brochure.

1.1.3. Epetraborole Clinical Experience

Epetraborole was originally being developed for treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) as an IV-to-oral switch regimen. As a result, between 2010 and 2012, 6 Phase 1 studies in healthy volunteers (4 IV epetraborole studies and 2 oral epetraborole studies) and 2 Phase 2 studies in patients (IV epetraborole) were initiated. The Phase 2 studies and two Phase 1 studies were stopped prematurely due to observations of emergent epetraborole resistance development in 3 Enterobacterales isolates in the Phase 2 cUTI study; subsequently, the development of epetraborole monotherapy for infections caused by Enterobacterales was discontinued. These studies evaluated epetraborole doses up to 4000 mg/day IV for 14 days and 6000 mg/day oral for 10 days. Epetraborole is now being developed to treat MAC lung disease, which accounts for approximately 80% of NTM lung disease in the US and Europe and approximately 93% in Japan (Izumi, 2019; Prevots, 2015). The oral dosages previously studied (up to 6000 mg/day) are substantially higher than the epetraborole 500 mg oral QD regimen proposed for further development for the treatment of MAC lung disease.

To date, epetraborole has demonstrated a profile that is generally well tolerated with linear PK characteristics. In the Phase 1 studies in which epetraborole was administered IV (up to 4000 mg/day for 14 days), there were no SAEs and no dose-limiting treatment-emergent adverse events (TEAEs). Variable decreases in reticulocytes and hemoglobin levels were observed, and these laboratory changes were reversible on dosing cessation. In the completed Phase 1 oral SAD/MAD (Study GSK LRS114470), dosages up to 4000 mg daily (2000 mg twice daily [BID]) for 10 days were generally well tolerated. Although there was some nausea, this was mitigated with food. The highest dosage cohort (6000 mg oral epetraborole daily, administered 3000 mg q12h) was terminated due to GI intolerability (eg, nausea, vomiting). In the earlier Phase 1 studies in which epetraborole was administered orally, there was a mild food effect in the fed state resulting in a ~15% decrease in exposures and ~1.5-hour delay in time to reach maximum plasma drug concentration (T_{max}).

The completed EBO-101 Phase 1b dose-ranging study supports the tolerability of oral epetraborole described above (at dosages of 250 mg to 1000 mg PO q24h or q48h for up to 28 days). The most common types of drug-related TEAEs in this study were GI events (eg, nausea, abdominal discomfort, diarrhea) and headache. Most (approximately 92%) TEAEs were mild; there were no severe or serious TEAEs in this study. This Phase 1b study also included a food effect cohort. In Study EBO-101, both epetraborole and metabolite M3 reached peak plasma concentrations rapidly, with median T_{max} within the ranges of approximately 1 to 3 hours and 2 to 3 hours, respectively. In the food effect cohort, the median T_{max} under fasted and fed

conditions for epetraborole was 0.5 to 2 hours and 2 to 3 hours, respectively; and 2 to 3 hours and 4 to 6 hours, respectively for metabolite M3.

Based on earlier Phase 1 and 2 epetraborole clinical studies using significantly higher EBO daily doses, gastrointestinal (GI) events and anemia were predetermined AESIs; GI events were the most common types of TEAEs in Study EBO-101 in both epetraborole and placebo-treated subjects, predominantly consisting of transient, mild events of nausea. Anemia was also identified as an AESI prior to the start of the study. The hematological effects of epetraborole were adequately characterized in EBO-101 and were consistent with those observed in previous Phase 1 and Phase 2 studies and nonclinical nonhuman primate studies. See details in Section 1.2.

All prior epetraborole studies are further detailed in the current Investigator's Brochure. The epetraborole dose rationale is described in Section 5.2.

1.2. Benefit/Risk

Details about the known and expected benefits and risks and including detailed description of TEAEs of epetraborole may be found in the current Investigator's Brochure.

For development of oral epetraborole in NTM lung disease, the dosage of epetraborole will be 500 mg QD. The exposure associated with this dose achieved a >90% probability of PK/pharmacodynamic (PD) target attainment for efficacy amongst 10,000 simulated patient PK profiles generated using Monte Carlo simulation.

Dose-related GI TEAEs are the most common types of TEAEs reported in epetraborole studies to date. Across the Phase 1 oral epetraborole studies, the most common AEs are GI in nature (nausea, vomiting, diarrhea) and headache. Oral epetraborole doses above 2000 mg (studied as 3000 mg q12h, 6000 mg daily) resulted in dose-limiting GI events. *Clostridioides difficile (C. difficile)*-associated diarrhea (CDAD) has not been reported with the use of epetraborole but has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents may alter the normal microbiota of the colon potentially leading to overgrowth of *C. difficile* and potential toxin production, which contribute to the development of CDAD.

Orthostatic hypotension and related TEAEs (syncope, presyncope, dizziness postural, and dizziness) were also common types of TEAEs in high-dose oral and IV epetraborole Phase 1 and 2 studies. In general, the rate of these types of events were similar to or slightly higher than those observed in placebo-treated subjects.

Across all oral and IV epetraborole Phase 1 and 2 studies to date, drug-related TEAEs of ALT and AST increases were observed in approximately 2% (each) of epetraborole-treated subjects. These ALT and AST elevations were asymptomatic, with no concomitant increases in total bilirubin levels. No cases of Hy's law have been described for subjects exposed to epetraborole to date.

In previous Phase 1 and Phase 2 studies, in addition to observations in nonclinical nonhuman primate studies, variable decreases in reticulocytes and hemoglobin levels were observed, and these laboratory changes were reversible on dosing cessation. In a 28-day dose-ranging Phase 1b study (EBO-101), hematological changes featured initial dose-dependent decreases in

reticulocyte levels (with nadirs around Day 8), followed by dose-dependent decreases in hemoglobin levels (with nadirs around Day 28). In EBO-101, one TEAE of asymptomatic, possibly-related anemia of moderate severity (based on the lowest hemoglobin level of 9.2 g/dL on Day 22, a Grade 2 decrease based on CTCAE [NIH, 2017]) was observed in the highest dose cohort (the single subject administered epetraborole 1000 mg q24h). Five additional epetraborole subjects experienced decreases of hemoglobin below the lower limit of normal (LLN) of the normal reference range, deemed not clinically significant by the study Investigator (2 of 6 epetraborole subjects in the 250 mg q24h cohort, and 3 of 6 epetraborole subjects in the 750 mg q24h cohort); however, some of these cases may have been confounded by concomitant TEAEs, such as upper respiratory tract infection, parainfluenza virus infection, iron deficiency, menstruation, and epistaxis. No hemoglobin levels decreased below the lower limit of normal in subjects treated with 500 mg q24h for 28 days; the largest mean decrease in hemoglobin values from baseline in the 500 mg q24h cohort was 13.5%—less than the maximum hemoglobin decreases predicted in the exposure-response model at the 99th percentile of simulated AUC exposure (17.6%). The cases of anemia in this study were normocytic and normochromic, and associated with a compensatory reticulocyte response during and after study drug administration. Available data suggest that epetraborole only affects erythropoiesis, and no other blood cell type generation pathway (including lymphocytes, basophils, eosinophils, neutrophils, monocytes, or platelets). Additional details on the hematological data from the Phase 1 epetraborole studies are available in the current Investigator's Brochure. Hemoglobin should be monitored on a regular basis in patients who receive epetraborole, and premature discontinuation or interruption of therapy with epetraborole should be considered in patients who develop or have worsening anemia. Guidance to Investigators on monitoring and managing anemia are provided in Section 5.5.2.4.

To date, epetraborole use in female patients has been very limited; therefore, use in pregnancy is contraindicated. It has not been established if epetraborole or its metabolites are excreted in breast milk. Due to observed findings in embryo-fetal development studies (see current Investigator's Brochure), all females of childbearing potential (FOCP) must commit to either sexual abstinence or use of at least 2 medically accepted, effective methods of contraception and male patients who are sexually active with a female partner of childbearing potential must agree to use an effective barrier method of contraception; as outlined in Inclusion Criterion 5. Of note, based on nonclinical data from drug-drug interaction studies, an interaction between epetraborole and hormonal contraceptives is not anticipated.

In summary, both oral and IV epetraborole have been associated with GI TEAEs and variable decreases in RBC parameters (eg, reticulocytes, hemoglobin), and both types of TEAEs (GI events and anemia) will be captured as AESIs in this study. The RBC changes observed in previous Phase 1 and Phase 2 studies were more frequent at higher doses and strictly limited to the erythroid cell lineage. The potential risk for substantial hematological effects associated with epetraborole tablets intended for study in patients with mycobacterial infection is considered to be low, as the targeted oral epetraborole dose for this indication is at the low end of the previously studied dosage range (500 mg daily), and no hemoglobin levels decreased below the lower limit of normal in subjects treated with 500 mg q24h for 28 days in the aforementioned Phase 1b dosing-ranging study. Hematological parameters are incorporated into eligibility criteria (Exclusion Criteria 4 and 5, Section 4.2) and premature discontinuation of study drug criteria (Section 4.4). This study also incorporates a DSMB—one of the members of which is a

Hematologist—to monitor unblinded, cumulative laboratory and TEAE data at regular intervals during the study (ie, after 25%, 50%, and 75% enrollment in both the Phase 2 and Phase 3 parts of the study). Importantly, monitoring of hematological parameters is a standard, easy-to-implement, routine laboratory evaluation that will ensure the safety of the patients in this study.

Overall, the Sponsor considers the emerging safety profile of epetraborole supportive of further clinical evaluation of epetraborole in patients for which there are unmet needs for new therapeutic options, such as treatment-refractory MAC lung disease.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Phase 2 Part of the Study

2.1.1. Objectives

2.1.1.1. 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 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

2.1.1.2. 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 $MACrO_2$ Patient-Reported Outcome (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], 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 PK of oral epetraborole, including an interim PK analysis to assess exposures from approximately the first 16 epetraborole-treated patients

2.1.1.3. 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 radiographic 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
- To evaluate the proposed symptom-based clinical response definition that uses the $MACrO_2$ PRO, and to understand patient perspectives on meaningful change more generally, through qualitative embedded interviews

2.1.2. Endpoints

2.1.2.1. 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 conversion monthly through Month 6 in the Micro-ITT Population. Sputum conversion will be assessed using culture conversion based on 3 consecutive monthly negative sputum cultures for MAC
- Assessment of TEAEs and changes from baseline in clinical laboratory values, electrocardiograms (ECGs), and vital sign changes in the Safety Population

2.1.2.2. Secondary Endpoints for Phase 2

- *[In the US:]* By-subject sputum conversion monthly through Month 6 in the Micro-ITT Population. Sputum 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, QOLB, 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 pathogen[s] different from the baseline MAC isolate) and relapse (pulmonary MAC infection caused by the same baseline MAC isolate) at Month 6, End of Therapy (EOT), and Late Follow-up (LFU) in the Micro-ITT Population
- Characterization of epetraborole plasma exposure in a population PK model

2.1.2.3. 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

2.2. Phase 3 Part of the Study

2.2.1. Objectives

2.2.1.1. 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

2.2.1.2. 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

2.2.1.3. 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 radiographic 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

2.2.2. Endpoints

2.2.2.1. 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 $\geq$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

2.2.2.2. 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 Population
- PRO symptom/function-based clinical response using mean changes in PRO domain scores (eg, QOLB, 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

2.2.2.3. 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. STUDY DESCRIPTION

3.1. Summary of Study Design

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.

Based on the qualitative results of patient interviews in a Concept Elicitation Study (Study AN2-001/EVA-29879-01), a gap analysis (EVA-29879-00), a recent Food and Drug Administration (FDA) Draft Guidance for Industry for developing drugs for treatment of pulmonary disease caused by MAC (FDA, 2021), PRO-based FDA guidance documents (FDA, 2009; FDA, 2020), and specific written FDA feedback, the Sponsor has developed a new PRO measure ($MACrO_2$ PRO) using an individualized symptom evaluation approach for key symptoms associated with treatment-refractory MAC lung disease (see Section 7.5.5.1). This study features a sequential Phase 2/3 approach with an initial Phase 2 assessment of symptom-based clinical responses, 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. Results from the Phase 2 part of the study will inform the specific PRO and the symptom-based clinical response definition to be used in the Phase 3 part of the study. In addition, a PK analysis from an initial group treated with epetraborole in the Phase 2 part of the study will assess oral epetraborole exposures in patients with treatment-refractory MAC lung disease.

In the Phase 2 part of the study, approximately 80 patients will be randomized in a 1:1 ratio (40 patients receiving active epetraborole tablets and 40 patients receiving matching placebo tablets) using an Interactive Responsive Technology (IRT) system and stratified by baseline use of ALIS and age at informed consent (<65 years versus ≥65 years). The Phase 2 part of the study includes a blinded psychometric analysis to assess the psychometric properties (ie, reliability, validity, ability to detect change [responsiveness], and clinically meaningful within-patient changes in scores) of a novel "$MACrO_2$ PRO" instrument. In addition, symptom-based clinical responses will be assessed using blinded data, to inform the measurement of clinical response in the Phase 3 part of the study. The Phase 2 psychometric data analyses will support selection and positioning of PRO measures as endpoints for Phase 3. Decisions will be based on item-level or domain-level (when appropriate) performance and ability to detect change (responsiveness) in Phase 2.

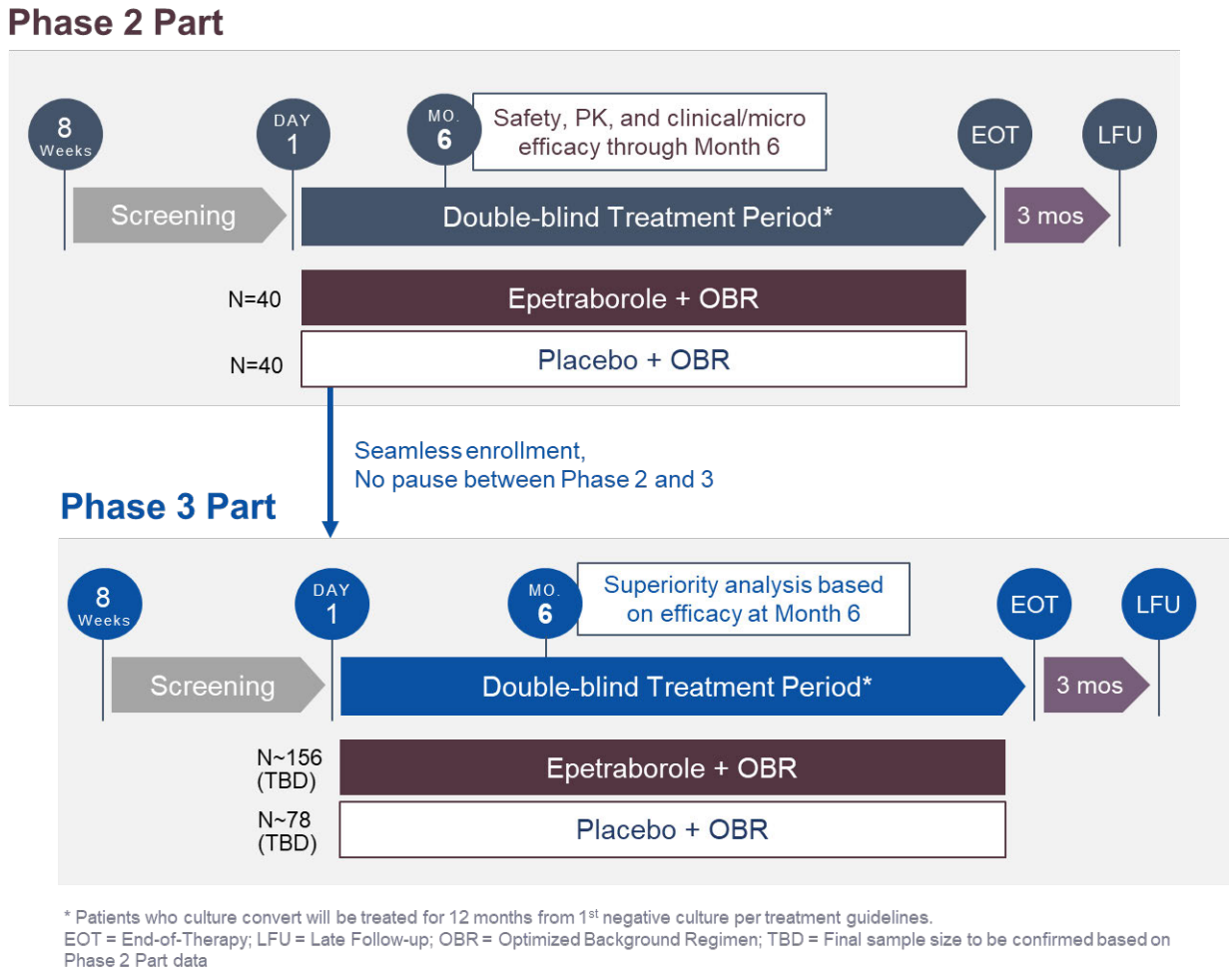
Up to 40 eligible patients in the Phase 2 part of the study will participate in an optional qualitative embedded interview to share their experience in the study. During the interviews, patients will be asked to discuss how each of their symptoms improved, worsened, or remained the same, and whether 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.

After the last patient in Phase 2 completes the Month 6+1 week PRO assessment, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for Phase 2 data analyses, but study staff conducting psychometric validation analyses will remain blinded. Patients, Investigators, and other study staff 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 clinical symptom responses, microbiological, safety, and PK data collected at multiple time points through Month 6. Patients enrolled in the Phase 2 part of the study will not be eligible for participation in Phase 3.

Figure 1 presents the study design.

Figure 1. Study Design



* Patients who culture convert will be treated for 12 months from 1st negative culture per treatment guidelines.
EOT = End-of-Therapy; LFU = Late Follow-up; OBR = Optimized Background Regimen; TBD = Final sample size to be confirmed based on Phase 2 Part data

The Phase 3 part of the study will test the superiority of epetraborole + OBR compared to placebo + OBR. In this part of the study, approximately 234 patients are planned to be randomized in a 2:1 ratio (156 patients receiving active epetraborole tablets and 78 patients receiving matching placebo tablets) using an IRT system and stratified by baseline use of ALIS and presence or absence of any fibrocavitary disease. The current symptom-based clinical response definition (using the $MACrO_2$ PRO) in Phase 3 is a placeholder to be verified after Phase 2 analyses, which will be based on data through Month 6. In addition, the Sponsor will determine if the sample size for Phase 3 should be adjusted and will confirm the Phase 3 epetraborole dosage regimen based on the observed plasma epetraborole exposure. Such changes will be addressed in a protocol amendment as appropriate. After the last patient in Phase 3 completes the Month 6 Visit, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for Phase 3 data analyses; patients, Investigators, and other study staff 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, microbiological, safety, and PK data collected at multiple time points through Month 6. All patients in the study will receive a minimum of 6 months of blinded study drug treatment. At the Month 6 Visit, all available sputum culture results will be assessed by the Investigator to determine whether a patient is a converter or non-converter. Patients who are assessed as converters will continue taking blinded study drug for 12 months after the first month that defines sputum culture conversion, up to a maximum of 16 months. Patients who are assessed as non-converters will discontinue study drug at the Month 6 Visit. See additional details in Section 3.1.1.

It is anticipated that the primary endpoint in the US will be $MACrO_2$ PRO symptom-based clinical response at Month 3 for the Phase 3 part of the study. However, whether this time point for the primary endpoint is at Month 3 or Month 6 will depend upon the psychometric evaluation of the PRO and the results of the Phase 2 part of the study. Outside of the US, the primary endpoint will be microbiological culture conversion by Month 6.

Study assessments and procedures will be completed at the following visits for both Phase 2 and Phase 3 parts of the study:

- **Screening Visit:** Screening assessments to determine study eligibility will be performed within 8 weeks prior to randomization as shown in Table 3 in Appendix A. Two to 3 sputum samples will be collected during Screening and may be collected on the same day or within a 5-day window beginning with collection of the first sample. See Section 7.5.3 for additional details.
- **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 Section 3.1.1.
  - During the first 6 months of the Treatment Period, study assessments (including microbiological, clinical, safety, and PK assessments) will be performed from Day 1 (calendar day of first dose of study drug) and every 28 days (±7 days) thereafter, up to Month 6 (Day 169 ±7 days).
  - Patients who culture-convert based on 3 consecutive monthly negative sputum cultures for MAC by Month 6 (Day 169 ±7 days) will continue blinded study drug for 12 months from the first month that defines sputum culture conversion up to a maximum of 16 months in total; see Section 3.1.1.
  - For patients continuing blinded study drug during the Treatment Period after Month 6, safety assessments will be performed monthly, and other assessments (including microbiological and clinical assessments) will be performed every 3 months (84 days ±7 days), up to EOT, as specified in Table 4 in Appendix A.
- **EOT Visit:** The EOT Visit will be performed within 7 calendar days after the last dose of study drug. Patients requiring more than the maximum 16 months of MAC lung disease treatment for any reason will be discontinued from study drug and treated with an appropriate open-label antimycobacterial regimen at the discretion of the Investigator. EOT will occur up to 12 months after the first negative sputum culture for MAC (ie, the first month that defines sputum MAC culture conversion), or

at the time of premature discontinuation of study drug for any reason, including continued positive cultures despite 6 months of study drug therapy or any time after achievement of culture conversion. The EOT assessments may be performed during a regularly scheduled clinic visit if within the EOT window. For patients who are withdrawn from the study prior to completion, all the EOT Visit procedures will be performed at an Early Termination (ET) Visit.

- **LFU Visit:** The LFU Visit will be performed 3 months (84 days ±14 days) after the last dose of study drug.

Patients who are prematurely discontinued from study drug for any reason will remain in the study (ie, will not be withdrawn from the study) to undergo all scheduled EOT and LFU assessments, including safety assessments.

Microbiological methods are described in Section 7.5.3 and additional details are presented in the Laboratory Manual.

3.1.1. Duration of Study Drug Administration and Study Participation

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 as described in Section 3.1.

Each patient's duration of study participation will vary depending on the timing of microbiological sputum MAC culture conversion. To receive study drug beyond Month 6, a patient must have achieved a microbiological sputum MAC culture conversion.

All patients will receive a minimum of 6 months of blinded study drug treatment. At the Month 6 Visit, all available sputum culture results will be assessed by the Investigator to determine whether a patient is a converter or non-converter. A converter is defined as a patient who has 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. A non-converter is a patient who does not have 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study.

Patients who are assessed as converters will continue taking blinded study drug for 12 months after the first month that defines sputum culture conversion, up to a maximum of 16 months. Patients who are assessed as non-converters will discontinue study drug at the Month 6 Visit. Patients who are discontinued from study drug at the Month 6 Visit will complete the EOT Visit at this time point, as well as the MACrO_2 and PGIS 1 week (+1 day) after their EOT Visit, and an LFU Visit 3 months (84 days ±14 days) after the last dose of study drug.

Because reporting of final respiratory culture and identification results may occur up to 8 weeks after specimen receipt at the regional or central microbiological laboratory, it is unlikely that the Month 5 culture results will be available at the Month 6 Visit. Patients who have negative culture results from Month 4 and no culture data available from Month 5 will be presumed to be converters and will continue blinded study drug at the Month 6 Visit. Such patients subsequently found to have positive cultures from the Month 5 and/or Month 6 visit must be discussed with the Medical Monitor for determination of continued study drug therapy beyond Month 6. Patients with *missing* sputum cultures from any visit prior to Month 6 should not be prematurely

discontinued from study drug or withdrawn from the study prior to discussion with the Medical Monitor to determine if study drug should be continued beyond Month 6.

Patients who have microbiological recurrence, defined as positive sputum culture(s) any time after experiencing sputum conversion, should be continued on blinded study drug until additional data (eg, antibiotic susceptibility results and/or molecular typing) are available to determine whether the positive culture is due to relapse or reinfection (see Section 7.5.3.4 for details regarding definitions and testing). Such cases should be discussed with the Medical Monitor *prior to* premature discontinuation of study drug (Section 4.4).

Unless the patient withdraws consent, patients who prematurely discontinue study drug will continue in the study for safety follow-up (ie, will not be withdrawn from the entire study) and will be assessed at the EOT and LFU visits.

3.1.1.1. Sites

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

3.1.2. 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 randomized patients (40 patients in the epetraborole + OBR group and 40 patients in the placebo + OBR group).
- The Phase 3 part of the study will consist of approximately 234 randomized patients (156 patients in the epetraborole + OBR group and 78 patients in the placebo + OBR group). The number of patients in the Phase 3 part of the study may be adjusted based on the results of Phase 2 analyses.

See Section 8.2.4 for further details.

3.2. Scientific Rationale for Study Design

The study design was based on the September 2021 draft FDA Guidance for Industry for developing drugs for the treatment of MAC lung disease (FDA, 2021), the most recent ATS/ERS/ESCMID/IDSA clinical practice treatment guidelines (Daley, 2020), and the CONVERT study design (Griffith, 2018), the latter being the only Phase 3 study conducted in the same patient subpopulation (ie, treatment-refractory MAC lung disease). Of note, ALIS is the only drug approved for treatment-refractory MAC lung disease, and the CONVERT study has been the only completed registrational Phase 3 study conducted in this patient population to date. In contrast to the open-label design of the CONVERT study, this EBO-301 study design is a double-blind, placebo-controlled assessment of epetraborole + OBR versus placebo + OBR. The OBR is the patient's standard-of-care combination regimen assigned by their treating physician, consisting of at least 2 antimycobacterial agents (per study eligibility criteria, see Section 4.1).

4. STUDY POPULATION

The eligibility criteria are the same for both the Phase 2 and Phase 3 parts of the study.

4.1. Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients who are 18 years of age or older.
2. Willing and able to provide written informed consent.
3. Patients with a diagnosis of treatment-refractory MAC lung disease, defined as respiratory specimen positive for MAC despite receiving a combination regimen of ≥2 antimycobacterial agents administered for ≥6 months, meeting all of the following (a) Microbiological, (b) Clinical, (c) Radiographic, and (d) OBR criteria:

   a. *Microbiological criteria*:

   - **Documentation of at least 1 *Pre-Study* MAC-positive respiratory specimen** (sputum or deep bronchial specimen) collected per standard of care within 6 months prior to signing the ICF; see Section 7.5.3.1 for details.
   - **At least 1 *Screening* MAC-positive expectorated or induced sputum sample.** See Section 7.5.3.2 for details, including enrollment of selected patients with a *pending* Screening culture result.

   b. *Clinical criteria*: At least 2 of the following patient-reported clinical symptoms, the "key" symptom of which must be of moderate or greater severity, ongoing at the time of randomization, according to the MACrO$_2$ PRO instrument (see Section 7.5.5.1):

      – Cough with sputum production
      – Cough without sputum (dry cough)
      – Chest congestion
      – Hemoptysis
      – Dyspnea (shortness of breath)
      – Fatigue
      – Night sweats or unusual sweating

   c. *Radiographic criteria:* Non-contrast chest CT scan within 6 months prior to signing the ICF (*Pre-Study* chest CT) or within the Screening Period (*Screening* chest CT) with abnormalities consistent with MAC lung disease based on local interpretation (eg, Investigator or local radiologist). See Section 7.5.1.4 for details, including allowable types of chest CTs.

   d. *OBR criteria:* An OBR is a combination regimen that consists of ≥2 antimycobacterial agents. The patient-specific OBR must be administered for a minimum duration of 6 consecutive months that is either ongoing at the time of Screening or was stopped or paused no more than 12 months before Screening (exceptions to treatment with OBR for 6 consecutive months may include changes to

dose level or frequency during therapy, replacement of a component of the background regimen with a member of the same drug class, and/or short [eg, approximately 6 weeks, cumulatively] interruptions of therapy).

Patients whose OBR was stopped prior to Screening must have a documented prior MAC-positive respiratory specimen despite receiving a combination regimen of ≥2 antimycobacterial agents for ≥6 months. At Screening, these patients must be restarted on an OBR consisting of ≥2 agents from their most recent regimen. The OBR regimen administered during Screening must be continued after randomization. See details in Section 5.7.1.

4. Patients who are willing to comply with all the study activities and procedures throughout the duration of the study, including willingness to continue OBR (ie, combination antimycobacterial treatment regimen including inhaled and parenteral medications, as appropriate, in addition to oral medications) and comply with all planned study visits and study procedures (including all planned sputum collections) from Screening through the LFU Visit (duration of study participation up to approximately 19 months, not including Screening).
5. Patients must agree to use an effective method of birth control, if applicable, as follows:
    a. FOCPs must commit to either sexual abstinence or use of at least 2 medically accepted, effective methods of birth control, which can be comprised of a combination of a highly effective method (eg, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections or locally approved method[s]; for example, of these, only oral contraceptive and indwelling intrauterine device are acceptable in Japan) and a barrier method (eg, condom or locally approved method[s]) from Screening through the EOT Visit and for 90 days following the last dose of study drug. Non-childbearing potential is defined as postmenopausal (ie, amenorrheic for at least 1 year) or surgically/naturally sterile.
    b. Male patients who are sexually active with a FOCP must agree to use an effective barrier method (ie, locally approved method[s]) of contraception from Screening through the EOT Visit and for 90 days following the last dose of study drug.
6. Patients expected to survive with continued antimycobacterial therapy and appropriate supportive care from Screening through the LFU Visit, in the judgment of the Investigator.

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in both the Phase 2 and Phase 3 parts of the study:

1. Patients with a presence of any suspected or confirmed disease or condition at Screening or the time of randomization that, in the opinion of the Investigator, may confound the assessment of symptom-based clinical response, including, but not limited to, the following:
    - Radiographic presence of any cavity >5.0 cm internal diameter (see Section 7.5.1.4)

- Cystic fibrosis or other inherited disorders of airway ciliary dysfunction (eg, primary ciliary dyskinesia)
- Active allergic bronchopulmonary mycosis
- Anticipated or planned lung surgery for treatment of MAC lung disease
- Disseminated MAC infection, or other known or suspected non-pulmonary source of infection (eg, infective endocarditis, osteomyelitis, meningitis, or urinary tract infection) requiring non-study antimicrobial therapy
- Concomitant pulmonary infection requiring antimicrobial therapy, including infection caused by fungi, viruses, non-MAC mycobacteria (eg, *Mycobacterium tuberculosis*, *Mycobacterium abscessus*, *Mycobacterium kansasii*), or other bacteria (eg, *Pseudomonas aeruginosa*, *Staphylococcus aureus*).

  Patients with MAC lung disease and concomitant non-MAC lung infection *requiring antimicrobial therapy* must complete the antimicrobial treatment prior to randomization. Patients with respiratory specimen cultures that contain growth of non-MAC organisms that are deemed by the Investigator to be respiratory tract colonizers and *who do not require or receive specific antimicrobial therapy* may remain eligible. The Investigator should discuss such cases with the Medical Monitor prior to randomization and provide rationale for study eligibility in the source document.

2. Patients with active pulmonary malignancy (primary or metastatic) or any malignancy that required or would require chemotherapy or radiation therapy within 1 year prior to randomization through the LFU Visit.
3. Patients with creatinine clearance (CrCl) of <30 mL/min, as estimated by the Cockcroft-Gault formula, at Screening:

   $$\text{Estimated CrCl (mL/min)} = (140 - \text{Age [years]}) \times \text{Actual Body Weight [kg]} \times [0.85 \text{ if Female}]) / (72 \times \text{Serum Creatinine [mg/dL]})$$

4. Patients with hemoglobin <10.0 g/dL or <6.2 mmol/L (Grade 2 anemia or worse, based on Common Terminology Criteria for Adverse Events [CTCAE; NIH, 2017]) at Screening; donation of blood or plasma within 28 days prior to randomization; or symptomatic loss of blood or hemorrhage within 28 days prior to randomization. Patients with an initial Screening hemoglobin of ≥10.0 g/dL to <LLN or ≥6.2 mmol/L to <LLN will be retested at the central clinical laboratory to confirm eligibility and results must be available prior to randomization.
5. Patients with severe hemoptysis within 28 days prior to randomization, defined as >100 mL (approximately >7 tbsp blood) over any 24-hour period or severe or extremely severe hemoptysis based on the MACrO$_2$ PRO at baseline.
6. Patients with severe hepatic impairment, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) or total bilirubin >2 × ULN, or clinical signs of cirrhosis or end-stage hepatic disease (eg, ascites, hepatic encephalopathy).

7. Patients who are pregnant or breastfeeding.
8. Patients with a mean QT interval corrected using Fridericia's formula (QTcF) >480 msec based on triplicate 12-lead ECGs at Screening.
9. Patients with an immunodeficiency or an immunocompromised condition and risk for an opportunistic pulmonary infection, including:
    - Known history of human immunodeficiency virus (HIV) infection *plus* either an active acquired immunodeficiency syndrome (AIDS)-defining illness in the past 12 months, or a known cluster of differentiation 4 (CD4) count <200/mm^3 within the past 12 months
    - Neutropenia at Screening (absolute neutrophil count <1,000 neutrophils/mm^3)
    - Use of immunosuppressive therapy at Screening that in the opinion of the Investigator may place the patient at risk for an opportunistic pulmonary infection, including transplant rejection medication and chronic systemic corticosteroids defined as ≥20 mg/day of prednisone or systemic equivalent for >4 weeks.
10. Patients with an anticipated start of new non-study antimycobacterial therapy to be administered at any time between Screening and EOT.
11. Patients who have participated in a clinical trial of an investigational agent within 30 days (or 5 half-lives, whichever is longer) prior to Screening.
12. Patients with any prior exposure to epetraborole.
13. Patients with any condition that, in the opinion of the Investigator, interferes with the ability to safely complete the study or adhere to study requirements, including the patient's inability or unwillingness to comply with all study assessments and visits.
14. Patients with a hypersensitivity to any epetraborole excipient (ie, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc).

For eligibility purposes, vital signs, clinical laboratory tests, and ECGs may be repeated once if an abnormal result is observed at the initial reading during Screening.

4.3. Withdrawal from Study

Participation of a patient in this clinical study may be discontinued for any of the following reasons, including, but not limited to:

- The patient withdraws consent or requests discontinuation from the study for any reason
- The patient is lost to follow-up (see Section 4.5)
- The patient fails to comply with Protocol requirements or study-related procedures
- The Investigator determines that it is in the best interest of the patient to withdraw from the study Protocol, for reasons other than an AE (eg, an occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the Protocol)

- The study is terminated or temporarily suspended by the Sponsor or a regulatory authority (see Section 8.4)

Patients who wish to withdraw completely from this study during the Treatment Period should be encouraged to undergo the EOT Visit safety and efficacy assessments at the time of withdrawal at an ET Visit.

Patients who withdraw from the study should be assessed as indeterminate at the most appropriate visit(s) at the time of withdrawal.

Patients who are withdrawn from the study will not be replaced.

4.4. Premature Discontinuation of Study Drug

Premature discontinuation of study drug by the Investigator is an important decision that should be discussed with the Medical Monitor, if feasible, before study drug is discontinued.

Possible reasons for premature discontinuation of study drug include, but are not limited to, the following:

- Occurrence of an AE that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study drug administration
- Grade 3 anemia or worse (hemoglobin <8.0 g/dL or <4.9 mmol/L) (see Section 5.5.2.4 for additional guidance, including guidance around temporary interruption of study drug)
- Hy's law criteria are met, defined by at least 3-fold elevations of ALT or AST >ULN, elevation of serum total bilirubin to >2 × ULN without elevated serum alkaline phosphatase, and no other disease or condition can be found to explain the liver test abnormalities
- Known pregnancy or breastfeeding during the study drug administration period
- Decline in postbaseline renal function with an estimated CrCl <30 mL/min (see Section 5.5.2.3 for additional guidance, including guidance around temporary interruption of study drug)
- Positive sputum cultures beyond Month 6 of therapy or at any time after achievement of culture conversion (see Section 3.1.1 for additional guidance)
- Requirement for addition of new non-study-specific antimycobacterial agents as rescue therapy for the index MAC infection
- Screening sputum sample cultures finalized as no growth (culture-negative) for MAC after randomization. Reporting of final respiratory culture and identification results may occur up to 8 weeks after specimen receipt at the regional or central microbiological laboratory.
- Study drug treatment interruption that exceeds 6 weeks

Unless the patient withdraws consent, patients who prematurely discontinue study drug will continue in the study for safety follow-up (ie, will not be withdrawn from the entire study) and

will be assessed at the EOT and LFU Visits. The reason for patient discontinuation of study drug must be documented in the electronic case report form (eCRF).

4.5. Patients Lost to Follow-up

For patients who are lost to follow-up, at least 3 documented attempts to contact must be made prior to the last scheduled contact (office or remote visit). One of these documented attempts must include a written communication sent to the patient's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return any unused study drug, if applicable, and return to the site for final safety evaluations. The return of unused study drug will be handled at the individual sites.

5. STUDY TREATMENTS

5.1. Treatment Groups

Eligible patients will be randomized to 1 of the following treatment groups:

- Epetraborole oral tablets 500 mg (two 250 mg oral tablets) QD + OBR
- Placebo oral tablets QD matched to epetraborole dosage + OBR

5.2. Rationale for Dosing

The proposed oral epetraborole dose for evaluation in this study is 500 mg administered QD. Epetraborole has a novel mechanism of action, inhibition of bacterial leucyl tRNA synthetase, which allows it to retain potency against isolates resistant to other MAC-active drugs. The MIC range of epetraborole against MAC is 0.25 to 8 µg/mL. Orally administered epetraborole was highly efficacious in the mouse chronic MAC lung infection model when tested at exposures that were approximately equivalent to the proposed human dose and against isolates with MIC values ≤8 µg/mL.

The PK/PD driver of efficacy for epetraborole is the AUC:MIC ratio as demonstrated in both in vivo previous studies with Gram-negative bacteria and in the HFM (hollow-fiber macrophage) system model with MAC. Plasma PK/PD targets for efficacy for MAC were derived from the mouse chronic MAC lung infection model. Plasma targets were used to define the dose to better correlate with the PK sampling schemes in patients described in this clinical study; however, the link between plasma and alveolar macrophage drug exposure has been established in a human Phase 1 intrapulmonary PK study. This study showed that epetraborole concentrates in alveolar macrophages at approximately 5 times higher exposures than in plasma.

A population PK model was developed for epetraborole and was used to construct 10,000 simulated PK patient profiles. These profiles included an inflated PK variance approach to accommodate a potentially larger range of AUC values observed in MAC lung disease patients compared to non-MAC lung disease patients and were used to determine the probability of achieving the anticipated exposures for efficacy in a simulated patient population. These analyses showed a high probability of achieving the median (100%) or highest (91.9%) observed 1-$\log_{10}$ kill PK/PD target with the 500 mg QD dose when dosed as monotherapy. However, 4.6- to 5.6-$\log_{10}$ bacterial kill was achieved when the drug was used in combination with a standard of care combination regimen for 56 days. A >90% target attainment was also achieved for the median PK/PD target and a 2-$\log_{10}$ kill threshold. These data suggest a high probability of achieving exposures at the site of infection in patients that have been associated with efficacy in nonclinical models of MAC lung disease.

The oral 500 mg QD epetraborole dosage was evaluated in the Phase 1b dose-ranging study (Study EBO-101). Epetraborole was generally well tolerated and there were no clinically significant abnormal hematological laboratory findings in the 500 mg QD cohort. In addition, an exposure-response model for hemoglobin suggests that mild reductions in hemoglobin may occur in some patients, and the expected levels are clinically manageable and reversible upon removal of study drug. No clinically meaningful changes have been observed in any human subject when administered the proposed human dosage for up to 28 days. Overall, the PO

500 mg QD dosage is expected to be efficacious in the target patient population while balancing the risk of hematological AEs.

5.3. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study; therefore, access to treatment allocation will be limited to unblinded members of the study team only. Treatment arm assignment will be blinded to patients, site study team, Sponsor study team, Contract Research Organization (CRO) study teams, and Investigators. Study drugs will be dispensed in a blinded fashion to the patients.

For the Phase 2 part of the study, a total of approximately 80 patients will be randomized in a 1:1 ratio (active epetraborole tablets: matching placebo tablets) using an IRT system and stratified by baseline use of ALIS and age at informed consent (<65 years versus ≥65 years). For the Phase 3 part of the study, a total of approximately 234 patients will be randomized in a 2:1 ratio (active epetraborole tablets: matching placebo tablets) using an IRT system and stratified by baseline use of ALIS and presence or absence of any fibrocavitary disease.

Blood samples will be collected from all patients in a blinded manner. Unblinded personnel will analyze the PK results.

After the last patients in Phase 2 and Phase 3 complete the Month 6+1 Week and Month 6 visits, respectively, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for data analyses; study staff conducting psychometric validation analyses will remain blinded. Patients, Investigators, and other study staff will also remain blinded to treatment assignment through the last study visit (LFU) (see Study Blinding Plan).

5.4. Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in emergencies where the identity of study drug is required for further treatment of the patient. Specifically, unblinding at the request of the Investigator should occur only in the event of severe AE or SAE that is reasonably assessed as drug-related and for which it is necessary to know the treatment arm assignment to determine an appropriate course of therapy for the patient. If the Investigator must identify the treatment arm assignment of an individual patient, the Investigator or qualified designee should request the treatment arm assignment from the centralized randomization system. The Investigator is advised to not reveal the treatment arm assignment to any other site, Sponsor, or CRO personnel.

Whenever possible, prior to proceeding with unblinding, the Investigator will contact the Sponsor to discuss the need to break the blind. The Investigator will notify the Sponsor as soon as it is practical in the event of the study blind being broken and the reason will be documented. In the event this is not possible, the Investigator should contact the Sponsor as soon as possible to discuss the event without revealing the treatment arm assignment. The Investigator must document the patient identification, the date and time of breaking the blind, and must clearly explain the reasons for breaking the blind.

Medically necessary care should not be delayed for unblinding information (ie, the Investigator should treat the patient based on the patient's signs/symptoms without waiting for the unblinding process to be completed).

Patients who are unblinded and discontinue study drug should continue to complete all safety assessments at subsequent study visits.

Data that may potentially unblind the treatment assignment (eg, epetraborole plasma concentrations, treatment allocation, or study drug preparation/accountability data) will be handled with special care during the data cleaning and review process. These data points will be handled in such a way that prior to unblinding, any data that may potentially be unblinded to study team personnel will be presented as blinded or will not be made available. In the case of the PK analysis of approximately 16 epetraborole-treated patients, a masked data transfer will be sent to the PK Data Review Committee. If applicable, unblinded data may be made available to unblinded quality assurance representatives or unblinded monitors for the purposes of conducting independent drug audits.

In the event that the treatment assignment is broken, the date, the electronic signature of the person who broke the code, and the reason for breaking the code will be recorded in the IRT system and the source documents. After breaking the blind and the patient is withdrawn from the study, the patient should receive follow-up for safety purposes. Any code-breaks that occur must be reported to the Sponsor. Code-break information is held by the pharmacist or designee at the site.

5.5. Study Drug - Epetraborole

5.5.1. Labeling, Packaging, Storage, and Handling

Epetraborole is provided for oral administration as a white to off-white modified-oval, film-coated, IR tablet containing 250 mg epetraborole as free base (288.5 mg as hydrochloride salt). Color-matched placebo tablets will also be provided.

5.5.1.1. Labeling

Labels containing study information and packing identification will be handled by the Sponsor. Space will be allocated on the label for the site representative to record a unique patient identifier. Additional labels (eg, those used when dispensing marketed products) may not be added without the Sponsor's prior full agreement in advance. Refer to the Pharmacy Manual for more details.

5.5.1.2. Packaging

Study drug will be packaged via Sponsor-approved vendors. Epetraborole tablets and placebo tablets are separately packaged in white, opaque, high-density polyethylene bottles with an enclosed desiccant and a child-resistant closure. Each bottle contains 30 tablets. Any changes to the Sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the Sponsor.

5.5.1.3. Storage

Epetraborole and placebo tablets should be stored as directed on the study drug label and as described in the Pharmacy Manual. The study drugs must be stored as above in a secure area with access limited to the Investigator and authorized staff. Study drug supplies will be stored securely under the appropriate conditions according to local standard operating procedures. The Investigator has overall responsibility for ensuring that the study drugs are stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or a member of the study team, but this delegation must be documented.

Temperature monitoring at the site will be required to ensure study drug is maintained within the required temperature range as directed on the study drug label and as described in the Pharmacy Manual. The Investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained. The temperature should be either monitored continuously by using an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific period can be recorded and retrieved as required. These devices (eg, certified minimum/maximum thermometer) would require manual resetting upon each recording. The Sponsor must be notified upon discovery of excursions from the established range in accordance with procedures described in the Pharmacy Manual. Temperature excursions not permissible per the study drug label or Pharmacy Manual will require site investigation as to cause remediation. The Sponsor will determine the impact of such excursions on the study drug and will provide supportive documentation as necessary. Under no circumstances should any study drug be dispensed to patients until the impact of such excursion is determined and the study drug is deemed appropriate for use by the Sponsor.

5.5.1.4. Handling

The Sponsor will provide a sufficient quantity of study drug supplies to each site. Sites must ensure that a responsible person correctly receives deliveries of study drugs from the Sponsor or Sponsor's clinical depot, that all receipts of drug shipments are recorded on the appropriate drug accountability forms, and that the study drugs are stored in a secure area in the required storage conditions. The Investigator will be responsible for ensuring that the integrity of packaged study drug is not compromised prior to dispensing. Only patients enrolled in the study may receive the study drugs, in accordance with applicable regulatory requirements. Only authorized and trained site personnel may handle, supply, or administer the study drugs.

Authorized and trained site personnel at each site will dispense the study drugs according to pre-defined drug dispensing requirements. For more details on the procedures for dispensing, refer to the Pharmacy Manual.

5.5.1.5. Study Drug Accountability

Drug accountability will be recorded at each study visit by count of remaining study drug tablets.

5.5.1.6. Study Drug Destruction or Return

Study drug reconciliation will be completed prior to initiating the destruction or return of study drug. All remaining study product (partially used, unused, damaged, and quarantined bottles) will be destroyed at the end of study in accordance with the site's standard operating procedures

or, if necessary, returned to distribution depot for destruction. Refer to the Pharmacy Manual for more details.

5.5.2. Study Drug Administration

Active epetraborole and matching placebo oral tablets will be administered at a dose of 500 mg QD. Study drug tablets should be administered in a fasting state (no food for at least 1 hour before and at least 2 hours after study drug administration). If GI upset occurs with study drug on an empty stomach, study drug may be taken with a small snack or administrated at bedtime to improve tolerability.

The first dose of study drug will be administered following randomization on Day 1 in the presence of the Investigator or designee. Following the first dose of study drug, patients will self-administer study drug orally QD. Refer to Section 5.5.2.3 for details regarding study drug dosing if a patient's CrCl decreases to <30 mL/min and Section 5.5.2.4 for details regarding study drug dosing if a patient's hemoglobin decreases to <10.0 g/dL or <6.2 mmol/L.

5.5.2.1. Interactive Responsive Technology and Allocation of Study Drug

An IRT system will be used for study drug management tasks. This may include randomization, study drug supply management, inventory management and supply ordering, study drug expiration tracking, and emergency unblinding.

Once informed consent has been obtained, patients will be assigned a unique 9-digit patient identifier at Screening.

The first approximately 80 patients of the study will be randomized for Phase 2 in a 1:1 ratio (40 patients receiving active epetraborole tablets and 40 patients receiving matching placebo tablets) using an IRT system. For the Phase 3 part of the study, approximately 234 patients are planned to be randomized in a 2:1 ratio (156 patients receiving active epetraborole tablets and 78 patients receiving matching placebo tablets) using an IRT system.

For this study, enrollment will occur at the time a patient is randomized. Randomization is described in Section 5.3.

5.5.2.2. Timing of Study Drug Dose Administration

The first dose of study drug should be administered as soon as possible following randomization on Day 1, in the presence of the Investigator or designee. Following the first dose of study drug, adjustments in the time of daily study drug administration are allowed to align with patient-specific medication dosing schedules in the management of treatment-refractory MAC lung disease; however, note that study drug will be administered in a fasting condition per Section 5.5.2. The administration of oral epetraborole with or without food was evaluated in a Phase 1 study to evaluate the safety, tolerability, PK, and food effect, see Section 1.1.3.

5.5.2.3. Study Drug Dosing in Patients With Normal Renal Function or Mild to Moderate Renal Impairment

Patients with CrCl <30 mL/min are excluded from the study (Exclusion Criterion 3), as the appropriate epetraborole dosage in patients with severe renal impairment or end-stage renal disease is unknown at this time. Upon enrollment into the study, patients will undergo regular

safety assessments, including routine monitoring of renal function (eg, serum creatinine) during the study.

Renal function, as estimated by CrCl, will be assessed using the Cockcroft-Gault formula and serum creatinine levels obtained at the central laboratory prior to Day 1 and as needed throughout the study per routine standard of care; in addition, CrCl will be programmatically determined from serum creatinine levels measured by the central laboratory.

Cockcroft-Gault formula:

$$\text{Estimated CrCl (mL/min)} = (140 - \text{Age [years]}) \times \text{Actual Body Weight [kg]} \times [0.85 \text{ if Female}]) / (72 \times \text{Serum Creatinine [mg/dL]})$$

Estimated CrCl should be calculated every time a local laboratory assessment of serum creatinine is performed. Actual weight in kilograms (not ideal weight) is required for the CrCl calculation. If available, the weight obtained on the day of the serum creatinine measurement should be used for calculating CrCl; however, the baseline weight or most recent weight may be used throughout the study for estimated CrCl calculations, if repeated weights cannot be obtained.

If the estimated CrCl decreases to <30 mL/min at any time after initiation of blinded study drug treatment, the Investigator should recheck creatinine values at the local laboratory to verify the result and administration of study drug should be temporarily discontinued if the result is verified. In such cases, testing for creatinine levels should be performed approximately every 1 to 2 weeks to determine whether study drug can be restarted. Treatment interruption should not exceed more than 6 consecutive weeks. Patients whose treatment interruption exceeds 6 weeks will be prematurely discontinued from study drug (Section 4.4) but remain in the study to undergo all scheduled EOT and LFU assessments, including safety assessments.

All clinically significant abnormal creatinine and CrCl values must be followed until repeat tests return to normal, stabilize, or are no longer clinically significant (Section 7.9.1). Once CrCl estimates improve to ≥30 mL/min, the case must be discussed with the Medical Monitor prior to restarting study drug. No dose adjustments are allowed based on renal function changes during the study.

5.5.2.4. Study Drug Dosing in Patients With Anemia

Patients with baseline hemoglobin <10.0 g/dL or <6.2 mmol/L (Grade 2 anemia or worse, based on CTCAE [NIH, 2017]) will be excluded from the study (see Exclusion Criterion 4). Decreases in RBC parameters (including hemoglobin, RBCs, and reticulocyte counts) have been reported in subjects receiving IV or oral epetraborole. In previous Phase 1 and Phase 2 studies of IV or oral epetraborole, reticulocyte decreases were observed within the first several days of dosing, followed by a decrease in hemoglobin (see current Investigator's Brochure for details). These hematological abnormalities appear to be transient, occur gradually, and when followed over time, return to baseline values after discontinuation of epetraborole.

Anemia is predefined as an AESI (Section 7.9.1.2). If anemia occurs during the study, the Investigator should recheck hematology values at the local laboratory to verify the result, and perform a workup to determine the cause of anemia according to his/her best clinical judgment (including, but not limited to, iron deficiency [eg, check a serum iron panel], GI bleeding, menstruation, concomitant medications [eg, non-steroidal anti-inflammatory drugs, rifamycins,

oxazolidinones, clofazimine], vitamin deficiencies [eg, vitamin B_{12}, folate], and hemolysis [eg, assess haptoglobin, blood smear]). As epetraborole has the potential to affect only erythropoiesis, and not the production of other blood cell types (eg, lymphocytes, basophils, eosinophils, neutrophils, monocytes, or platelets), anemia with concomitant decreases in white blood cells or platelets should prompt investigation of other potential causes.

If Grade 3 anemia or worse (hemoglobin <8.0 g/dL or <4.9 mmol/L) is identified at any time after initiation of blinded study drug treatment, the Investigator should recheck hematology values at the local laboratory to verify the result and perform a workup to determine the cause of the anemia as described above. If postbaseline Grade 3 anemia or worse is considered by the Investigator to be related to blinded study drug, administration of study drug should be temporarily interrupted. Interruption should not exceed more than 6 consecutive weeks. Patients whose temporary interruption exceeds 6 weeks will be prematurely discontinued from study drug (Section 4.4) but remain in the study to undergo all scheduled EOT and LFU assessments, including safety assessments. In such cases, hemoglobin levels should be monitored approximately every 1 to 2 weeks to ensure improvement by at least 1 grade.

All clinically significant abnormal hematology values must be followed until repeat tests return to normal, stabilize, or are no longer clinically significant (Section 7.9.1). After improvement or resolution of anemia occurs, the case must be discussed with the Medical Monitor prior to restarting study drug. No dose adjustments are allowed based on hematological changes during the study.

5.5.2.5. Dosing Interruptions, Incomplete Doses, and Missed Doses

All instances of noncompliance, defined as receipt of <80% or >120% of the anticipated number of doses of oral study drug dosed QD will be documented as protocol deviations.

If dosing is interrupted or incomplete, no adjustment to the dosing schedule is required.

If dosing is missed for any reason, the next planned dose should be administered as quickly as possible at the time of discovery, and the remainder of the doses should be administered at the pre-planned daily intervals starting with the following day (ie, the previous dosage schedule should remain unchanged).

Investigators should discuss continued study drug administration options after incomplete or missed doses with the Medical Monitor on a case-by-case basis. Case discussion with the Medical Monitor is required prior to re-initiation of study drug after interrupted dosing. Patients should not be prematurely discontinued from study drug based on compliance prior to discussion with the Medical Monitor.

5.6. Placebo

Color-matched placebo tablets will be provided by the Sponsor. The active and placebo tablets are packaged separately, as described in the study Pharmacy Manual.

5.7. Optimized Background Regimen

5.7.1. OBR Prior to Randomization

In this study, an OBR is a combination regimen that consists of ≥2 antimycobacterial agents per current ATS/ERS/ESCMID/IDSA treatment guidelines (Daley, 2020). The OBR is per standard of care, at the discretion of the Investigator, and not defined by the Sponsor or this Protocol.

The patient-specific OBR must be administered for a minimum duration of 6 consecutive months that is either ongoing at the time of Screening or was stopped or paused no more than 12 months before Screening. Exceptions to treatment with OBR for 6 consecutive months may include changes to dose level or frequency during therapy and/or short (eg, approximately 6 weeks, cumulatively) interruptions of therapy. Replacement of a component of the background regimen with a member of the same drug class is allowed.

Patients whose OBR was stopped prior to Screening must have a documented prior MAC-positive respiratory specimen despite receiving a combination regimen of ≥2 antimycobacterial agents for ≥6 months. At Screening, these patients must be restarted on an OBR consisting of ≥2 agents from their most recent regimen. The OBR regimen administered during Screening must be continued after randomization, with no anticipated need for additional antimycobacterial agents between Screening and EOT.

5.7.2. OBR Post Randomization

Throughout the duration of the study, patients should continue the same, multidrug (≥2 antibiotics), antimycobacterial OBR. This OBR should be guided by recommendations in the ATS/ERS/ESCMID/IDSA clinical practice treatment guidelines (Daley, 2020) and should not change during the Treatment Period except for safety concerns or in the event of microbiological failure (see Section 5.8.3). It is acceptable to remove an antimycobacterial agent from the OBR for any reason (eg, poor tolerability, emergence of resistance, drug holiday) as long as the remaining OBR contains at least 2 antimycobacterial agents. The Investigator must discuss further treatment with the Medical Monitor when removal of an agent (or agents) would reduce the OBR to a single agent.

Any patient who requires addition of new non-study-specific antimycobacterial agents as rescue therapy for the index MAC infection will have study drug discontinued (Section 4.4) but will remain in the study (ie, they will not be withdrawn from the study) to undergo all scheduled EOT and LFU assessments, including safety assessments.

Changes in the dosages of existing antimycobacterial agents, and replacement of a component of the background regimen with a member of the same drug class are allowed per Investigator discretion.

The Investigator is encouraged to discuss specific OBR scenarios with the Medical Monitor.

5.7.3. Guidance for Investigators: ALIS Use Before and During the Study

For ALIS use at baseline, the following must be considered:

- If ALIS has not been administered prior to study enrollment: As ALIS is recommended for use in treatment-refractory MAC lung disease according to the

current treatment guidelines (Daley, 2020), the Investigator and potential patient must consider its use instead of study enrollment. If the decision is made to enroll the patient in this study without prior administration of ALIS therapy, the rationale for not administering ALIS must be clearly stated in the source documentation (eg, patient decision, Investigator decision, contraindication to use, not available, high *a priori* likelihood that patient will not tolerate ALIS). Neither ALIS nor any other new MAC-specific therapy, other than blinded study drug, can be started during the treatment phase of the study (see Exclusion Criterion 10).

- If ALIS was administered prior to study consideration and will be continued during the study: The patient may remain eligible for the study provided the microbiological criteria (Inclusion Criterion 3.a) are met.
- If ALIS was administered prior to study consideration and subsequently discontinued for any reason: The patient may remain eligible for the study provided the microbiological criteria (Inclusion Criterion 3.a) are met and ALIS was discontinued at least 30 days prior to randomization.

5.8. Prior and Concomitant Medications and Prohibited Treatment

5.8.1. Prior Therapy

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 8 weeks prior to the date and time of first dose administration of study drug. Any patient record of prior treatment must be documented in the appropriate eCRF.

5.8.2. Concomitant Therapy

Concomitant medications or treatments administered between the dates and times of the first dose of study drug and the last study visit, inclusive, are to be listed in the appropriate eCRF.

With the exception of prohibited concomitant medications discussed in Section 5.8.3, other concomitant medications, including other antibiotics and vaccines, are permitted.

5.8.3. Prohibited Prior and Concomitant Therapy

The following medications and treatments are prohibited:

- Any anticipated or planned lung surgery for MAC lung disease
- Immunosuppressive therapy use at Screening and throughout the Treatment Period that in the opinion of the Investigator may place the patient at risk for an opportunistic pulmonary infection, including transplant rejection medication and chronic systemic corticosteroids defined as ≥20 mg/day of prednisone or systemic equivalent for >4 weeks. Short-term use of corticosteroids (eg, glucocorticoid taper for treatment of COPD exacerbation) is allowed.
- Chemotherapy or radiation therapy within 1 year prior to randomization through the LFU Visit

- The addition of a new non-study-specific, antimycobacterial therapy (eg, macrolides, rifamycins, ethambutol, aminoglycosides, fluoroquinolones, oxazolidinones, trimethoprim-sulfamethoxazole, clofazimine, isoniazid) to treat the index MAC infection is not allowed for reasons other than microbiological failure.

  If the Investigator believes that a potentially MAC-active agent is required to treat a non-MAC infection, the case should be discussed with the Medical Monitor prior to administration. Premature discontinuation of study drug or withdrawal from study should be avoided in these cases. See Section 5.7 for OBR details.
- Participation in a clinical trial of an investigational agent within 30 days (or 5 half-lives, whichever is longer) prior to Screening and throughout the Treatment Period

The use of concomitant drugs with the potential to cause anemia should be avoided when feasible. Any questions regarding the use of concomitant non-study-specific therapy should be directed to the Medical Monitor prior to administration.

Any patient who receives prohibited therapy will be excluded from the Per-Protocol Population; see the SAP(s) for more details.

6. STUDY PROCEDURES

Study procedures will follow the Schedule of Assessments (Appendix A). See Section 7 for details.

7. STUDY ASSESSMENTS

Refer to the Schedule of Assessments (Appendix A) for timing of assessments listed herein.

All visits are encouraged to be conducted in person; however, home health care is allowed (if available) as follows if it is not possible for the patient to be seen at the clinic (eg, unforeseen circumstances, intercurrent illness, travel, temporary relocations):

- *Must be conducted in person:* Screening and Randomization visits (Screening PROs may be completed at home)
- *All reasonable efforts should be made to conduct in person but home health care will be supported, if needed:* Month 6 and EOT visits
- *May be conducted in person or by home health care, if available:* all other visits per Appendix A

In the event of unforeseen circumstances (eg, a global pandemic), Investigators are encouraged to engage with their governing Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated. Attempts should be made to conduct safety monitoring and other efficacy assessments even if on-site visits are not possible. Sites shall discuss any expected modifications to the protocol visit schedule or assessments with the Sponsor to protect study participants and manage study conduct.

7.1. Informed Consent

See Section 10.3.

7.2. Inclusion/Exclusion Criteria

Patients must meet all inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) to be eligible for participation in the study. See Section 7.5.2 for instructions on confirming eligibility in patients with an initial Screening hemoglobin of ≥10.0 g/dL to <LLN or ≥6.2 mmol/L to <LLN. After confirmation of a patient's eligibility, randomization may occur per Section 5.3.

For eligibility purposes, vital signs, clinical laboratory tests, and ECGs may be repeated once if an abnormal result is observed at the initial reading during Screening.

7.3. Demographic Information

Demographic data (age, sex, race, ethnicity) will be collected and recorded.

7.4. Medical/Surgical History

Any medical condition or signs/symptoms already present at the time of first dose of study drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs/symptoms present at baseline changes in severity, frequency, or seriousness at any time after administration of the first dose of study drug (see Section 7.9.1). In this case, it should be reported as an AE.

7.5. Safety and Efficacy Assessments

7.5.1. Tests and Examinations

7.5.1.1. Physical Examinations

A physical examination 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. Physical examinations will be performed before the administration of study drug at the treatment visits. All clinically significant findings must be recorded in the eCRF as either a Medical History or as an AE.

7.5.1.2. Vital Signs, Height, Weight, and BMI

Vital signs will be measured at Screening and every scheduled study visit. Vital signs will include temperature, heart rate, and blood pressure. Wherever possible, vital signs will be obtained after at least 5 minutes resting in a supine or sitting position. All findings must be recorded in the eCRF. Height (at Screening only; without shoes), weight, and body mass index (BMI) will also be measured and recorded at the time points specified in Appendix A.

For eligibility purposes, vital signs may be repeated once if an abnormal result is observed at the initial reading during Screening.

7.5.1.3. 12-lead ECGs

Twelve-lead ECGs will be conducted at the time points specified in Appendix A.

[Outside of Japan:] At the Screening Visit, triplicate ECGs will be obtained within an approximate 15-minute period, separated by approximately 1 minute. On Day 1, a standard single 12-lead safety ECG will be collected between the first dose of study drug and the blood PK sample (2 to 3 hours after dose administration). At other scheduled visits, a standard single 12-lead safety ECG will be collected without regard to study drug timing.

[In Japan:] At the Screening Visit, triplicate ECGs will be obtained within an approximate 15-minute period, separated by approximately 1 minute. At all other visits, standard single 12-lead safety ECGs will be performed. The ECGs on Day 1 and at Months 2, 4, and 6 should be collected 1 to 3 hours after study drug administration, the approximate time at which maximum epetraborole concentration (T_{max}) is expected; thus, patients should be instructed to take the study drug before their scheduled ECG at Months 2, 4, and 6.

ECGs will be obtained after at least 5 minutes resting in a supine or semi-recumbent position. All findings must be recorded in the eCRF.

For eligibility purposes, ECGs may be repeated once if an abnormal result is observed at the initial reading during Screening.

7.5.1.4. Radiographic Assessments (Chest CTs)

Chest CT scans will be evaluated to assess eligibility and pulmonary radiographic response during the study. All chest CTs must be non-contrast and consist of contiguous sections through the lungs, each section of ≤3 mm thickness. Low-dose CT scans are acceptable.

Pre-Study chest CTs performed per standard of care may be used to determine eligibility if taken within 6 months of signing the ICF and will serve as the *Screening* chest CT. If the most recent *Pre-Study* chest CT was taken >6 months prior to signing the ICF, a chest CT must be obtained within the Screening Period (*Screening* chest CT).

The interpretation of *Screening* chest CTs (to assess for abnormalities consistent with MAC lung disease, per Inclusion Criterion 3.c) will be performed locally by the site (eg, Investigator or local radiologist). The Investigator is encouraged to review the CT with the local radiologist in cases where cavity size is close to the 5 cm exclusion (see Exclusion Criterion 1).

Radiographic response will be evaluated based on severity, extent of pulmonary disease, and overall improvement between baseline (ie, *Screening* CT scan) and Month 6 and between baseline and EOT. These evaluations and interpretations of digital images of chest CTs will be performed centrally by a member of an independent team of blinded radiologists. A minimum of 8 weeks between 2 chest CT scans is recommended. For example, if EOT occurs before Month 6, the EOT chest CT should be scheduled to occur at least 8 weeks after the *Screening* chest CT. If the last dose of study drug occurs within 8 weeks after the Month 6 chest CT, the EOT chest CT should be scheduled to occur at least 8 weeks after the Month 6 chest CT.

7.5.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the time points specified in Appendix A. Hematology and chemistry (per Appendix B) will be performed for all patients at the initial Screening Visit (ie, Days -56 to -15) to confirm eligibility.

Patients with an initial Screening hemoglobin of ≥10.0 g/dL to <LLN or ≥6.2 mmol/L to <LLN will have their hemoglobin retested at the central clinical laboratory for confirmation of eligibility and results must be available prior to randomization. Patients with hemoglobin <10.0 g/dL or <6.2 mmol/L (Grade 2 anemia or worse) are not eligible to participate in the study.

All clinical laboratory samples collected for eligibility and safety evaluations will be analyzed by a certified central clinical laboratory. See Appendix B for a list of clinical laboratory analytes.

Clinical laboratory evaluations required to confirm eligibility (ie, inclusion/exclusion criteria) include:

- Serum creatinine (for calculation of CrCl using the Cockcroft-Gault formula)
- Hemoglobin
- ALT
- AST
- Total bilirubin
- Absolute neutrophil count
- CD4 count (if HIV-positive and unknown CD4 count within the past 12 months; taken from medical history)
- Serum pregnancy test (only if FOCP)

For eligibility purposes, clinical laboratory tests may be repeated once if an abnormal result is observed at the initial reading during Screening.

Day 1 clinical safety laboratory evaluations should be collected prior to the first dose of study drug on Day 1. Following study drug dosing, the Investigator will review laboratory values for those outside of normal range and will be required to conduct clinically appropriate follow-up procedures. Clinical significance of the values outside of normal ranges will be assessed by the Investigator.

7.5.2.1. CrCl Calculation

See Section 5.5.2.3.

7.5.2.2. ADH Genotyping

ADH genotyping will occur on Day 1. ADH genetic variants will be tested to determine effects on PK analysis results; the results are not needed prior to dosing and will not impact study eligibility.

7.5.3. Sputum Collection and Microbiological Assessments

7.5.3.1. Pre-study Collection and Enrollment Criteria

At least 1 *Pre-Study* MAC-positive respiratory specimen must have been collected within the 6 months prior to signing the ICF. This *Pre-Study* respiratory specimen may be an expectorated or induced sputum sample, or a deep bronchial sample (eg, bronchoalveolar lavage, bronchial brush, or lung biopsy).

7.5.3.2. Collection and Testing During Screening

Two to 3 expectorated or induced *Screening* sputum samples should be collected within the 8 week Screening Period (after the ICF is signed). If a patient is unable to produce sputum spontaneously, 1 induced sputum specimen at the site will be acceptable. Sputum samples may be collected on the same day or within a 5-day window beginning with collection of the first sample. The *Screening* sputum samples will be sent to the regional or central microbiological laboratory for mycobacterial culture, identification, and quantification. Susceptibility testing and molecular testing (if applicable) of isolates will be performed at the central microbiology laboratory. The 8-week Screening Period allows for culture and identification of MAC isolates. Only identification to MAC level is required for randomization. Antimycobacterial susceptibility and molecular testing results (if applicable) are not required prior to randomization. See the Laboratory Manual and testing details in Section 7.5.3.4.

If the *Pre-Study* MAC-positive respiratory specimen was collected >8 weeks to 6 months prior to signing the ICF, the patient may be enrolled only after at least 1 of the *Screening* sputum samples is reported as MAC-positive by the regional or central microbiological laboratory.

If the *Pre-Study* MAC-positive respiratory specimen was collected within 8 weeks prior to signing the ICF and the patient was taking OBR at the time the specimen was collected, the patient may be enrolled in the study (at the Investigator's discretion) after collection of the *Screening* sputum sample(s) and a pending *Screening* culture result. If the *Screening* sputum sample culture(s) is finalized as MAC-negative *after* randomization, the patient will be

prematurely discontinued from study drug at the time that the final *Screening* sputum culture is reported as negative, and their OBR will be continued at the Investigator's discretion; however, they will remain in the study (ie, they will not be withdrawn from the study) to undergo all scheduled EOT and LFU assessments, including safety assessments.

7.5.3.3. Collection After Randomization

Post-randomization, 2 to 3 sputum samples will be collected at each visit per Appendix A and may be collected on the same day or within a 5-day window beginning with collection of the first sample. Induced or expectorated sputum samples are required at all time points. Sputum samples may be collected at the site or obtained by the patient at home after training by site personnel on the proper sputum collection and storage techniques. If a patient is clinically improving and no longer coughing or producing sputum, every effort should be made to collect sputum samples using sputum induction techniques. Sputum specimens will be refrigerated, not frozen, without fixatives or preservatives until shipped to the regional or central microbiological laboratory as outlined in the Laboratory Manual. If at least 1 of the sputum samples collected is MAC positive, the patient will be considered positive for MAC at that time point. If a sputum sample could not be collected despite reasonable efforts (eg, due to a non-productive cough or resolution of cough), the reason(s) the sputum was not collected should be documented in the source records. Patients with missing sputum samples should not be prematurely discontinued from study drug or withdrawn from the study prior to discussion with the Medical Monitor.

7.5.3.4. Testing

Sputum samples collected during the Screening Period and at designated time points during the study will be sent to the regional or central microbiological laboratory for mycobacterial culture, identification and quantification. Susceptibility testing and molecular testing (if applicable) of isolates will be performed at the central microbiological laboratory.

The time from receipt of sputum at the regional or central microbiological laboratory to a MAC-positive culture averages 3 weeks but may take up to 6 weeks. In addition, identification of MAC isolates to the species level using the line probe assay (LPA) or matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, averages 1 to 3 days. Isolates that cannot be identified or speciated using LPA or MALDI-TOF will be identified and speciated via sequencing of the *rpoB* gene or 16S rRNA, which takes up to an additional 7 days.

Microbiological evaluation of sputum samples will include improvement in quantitative colony counts. Quantification of bacteria via colony counts on solid agar will be performed and assigned a categorical score similar to that reported by Griffith, et al. where colony counts were predictive of symptomatic and radiographic improvement (Griffith, 2015) (see Table 1). An improvement in quantitative culture counts will be defined as a reduction in ≥1 categorical score from the screening isolate and the previous month's categorical culture score.

Table 1: Categorical Scoring for Quantitative Culture Counts

Colonies (CFU/mL)	Categorical Culture Score[a]
No growth on agar or broth	0
Growth in broth only	1
1-49	2
50-99	3
100-199	4
200-299	5
≥300	6

Abbreviation: CFU = colony-forming units.
[a] Categorical scores based on those reported in Griffith, 2015.

The regional and/or central microbiological laboratory will follow standardized methods and procedures for MAC culture, identification, and susceptibility testing (following CLSI guidelines). All respiratory culture specimens will be cultured in appropriate liquid and solid media. If the results are negative on solid media, the liquid media will be held for 6 weeks before reporting the culture as negative.

Standard antibiotic susceptibility testing will be performed using the most recent CLSI guidelines at the central microbiological laboratory. Epetraborole MIC values will not be reported to local sites during the study. Decreases in susceptibility of postbaseline isolates to epetraborole will be determined based on an increase in MIC values of ≥4-fold above those obtained at baseline. Postbaseline isolates with decreased susceptibility and the corresponding baseline isolate will be retested twice to confirm MIC values. If the result is confirmed, molecular testing may be performed to determine relatedness of the postbaseline and baseline isolates.

Molecular testing, including whole genome sequencing, may be performed to determine genetic relatedness of select baseline/postbaseline isolates. Analyses include, but are not limited to, comparison of patients' postbaseline MAC isolates to the baseline MAC isolate to determine if isolates are clonal and suggestive of persistent infection, relapse, or reinfection with an isolate of a different genotype. In this study, as per the NTM Network European Trials Group consensus statement on NTM treatment outcome definitions, "reinfection" is defined as a new pulmonary MAC infection caused by strain(s) different from the baseline MAC strain, and "relapse" is defined as pulmonary MAC infection caused by the same baseline MAC strain (van Ingen, 2018). Whole genome sequencing may also be utilized to evaluate the presence of genetic markers of antibacterial resistance.

Additional details, including instructions for collecting, processing, and shipping sputum specimens, will be provided in the Laboratory Manual.

7.5.4. Plasma PK Sampling and Assessments

Blood samples for PK analyses will be collected from all patients in a blinded manner. Blood samples will be collected in a fasted state as listed in Table 2. See Section 8.2.3 for further details.

Table 2: Pharmacokinetic Sampling Times

Sample	Sampling Time
Sample 1	2 to 3 hours after the Day 1 dose, while the patient is still fasting[a]; patient may eat after PK sample is obtained
Sample 2[b]	Within 1 hour before the Day 29 dose, while the patient is fasting[a] • Patients must be reminded not to take the Day 29 dose prior to the study visit • Patients should report the estimated time and date of their last dose prior to the Day 29 sample; record estimated time and date of the dose. • The Day 29 dose will be held until PK Sample 2 is collected. PK Sample 2 should be collected even if the dose is accidentally taken prior to sample collection; record actual time of the dose.
Sample 3[b]	2 to 3 hours after the Day 29 dose, while the patient is still fasting[a]; patient may eat after PK sample is obtained

EDC = electronic data capture; PK = pharmacokinetic.

[a] Fasting = No food for at least 1 hour before and at least 2 hours after study drug administration.

[b] If a patient is unable to complete either or both of the scheduled Day 29 PK blood draws, these samples may be obtained at a subsequent visit as unscheduled PK samples. Preferably, both Samples 2 and 3 will be obtained on the same day. In circumstances when *either* Sample 2 or Sample 3 (but not both) were previously collected, the missing sample alone may be collected at a subsequent visit. The date and time of each unscheduled blood draw should be recorded in the EDC system along with the estimated date and time of the last dose of study drug taken before the PK sample.

Plasma PK samples obtained from the epetraborole group will be analyzed using a validated assay by a central bioanalytical laboratory. Samples from placebo-treated patients will not be analyzed. The methods to be employed for the PK analyses will be presented in a data analysis plan and results reported in a separate PK report.

7.5.5. Patient-Reported Outcome Measures

An electronic PRO system will be used during the study to allow patients to complete the study questionnaires.

In both the Phase 2 and Phase 3 parts of the study, each patient will complete the following PRO measures:

- $MACrO_2$
- QOL-B
- NTM Symptoms Module
- SGRQ-C
- Global assessment scales (Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change [PGIC])

The Investigator will complete the Clinician Global Impression of Severity (CGIS) and Clinician Global Impression of Change (CGIC).

The PROs will be completed at the time points specified in the Schedule of Assessments (Appendix A). On Day 1, PROs should be completed prior to study drug administration, and will serve as the baseline assessment for comparison to on-treatment assessments. The $MACrO_2$, QOL-B, NTM Symptoms Module, SGRQ-C, and PGIS will be completed twice before the first

dose of study drug (ie, once between Days -14 and -7 and on Day 1 prior to study drug administration) to assess test-retest reliability. The $MACrO_2$ and PGIS will be completed at additional time points to further assess test-retest reliability. For patients whose EOT Visit coincides with the Month 3 or Month 6 visit, the $MACrO_2$, and PGIS will be completed 1 week (+1 day) after the EOT Visit. PRO test-retest reliability will be assessed in Phase 2 and may be analyzed in Phase 3 if deemed necessary.

7.5.5.1. $MACrO_2$ Patient-Reported Outcome Measure

The $MACrO_2$ PRO will be psychometrically evaluated in a blinded manner in the Phase 2 part of the study and a formal psychometric analysis plan will be developed. The planned analyses will include item-level performance (distribution of responses, missing data, and floor and ceiling effects); construct validity (including known-groups and concurrent validity); test-retest reliability; sensitivity to change; and defining meaningful change thresholds (ie, using global anchor items and clinical outcomes to define response). The $MACrO_2$ PRO measure may be further refined following the psychometric analyses or embedded interviews. The selection of the final PRO measure to use as the primary endpoint (in the US) or key secondary endpoint (outside the US) in the Phase 3 portion of the study and the timing of this assessment will be based on the $MACrO_2$ PRO item performance and sensitivity to change by treatment outcomes.

Patients will complete all 7 symptom items from the $MACrO_2$ PRO measure (Appendix C) at all study assessment time points specified in the Schedule of Assessments (Appendix A), regardless of the presence or absence of symptoms. During the Day -14 to -7 Screening Visit and on Day 1 (prior to dosing), patients will select which symptom that they rated as moderate, severe, or extremely severe that they most want to see improved to help understand the "key" symptom for each individual patient (ie, via $MACrO_2$ PRO Item 8). The severity of all symptoms on Day 1, as well as the "key" symptom identified on Day 1, will be defined as the baseline assessment for determination of clinical response in postbaseline visits. Symptom-based clinical response is defined as improvement of ≥1 grade in the key symptom with no worsening of ≥1 grade of other symptoms, according to the $MACrO_2$ PRO.

7.5.5.2. Quality of Life-Bronchiectasis

Patients will complete the QOL-B (Appendix D) at all study assessment time points specified in the Schedule of Assessments (Appendix A). The QOL-B questionnaire is a self-administered PRO measure designed specifically for patients with bronchiectasis. This PRO contains 37 items on 8 domains to assess respiratory symptoms, functioning, and health-related quality of life of patients within the past week (Quittner, 2015). Each domain score can range from 0 to 100 (with higher scores indicating better health-related quality of life). The recall period is 1 week, and each item uses a 4-point Likert scale.

7.5.5.3. Nontuberculous Mycobacteria Module

The NTM Module (Appendix E) will be completed at all study assessment time points specified in the Schedule of Assessments (Appendix A). The NTM Module generates 4 domain scores (0 to 100; higher scores indicate better functioning) reflecting NTM-specific symptoms (NTM Symptoms, Body Image, Digestive Symptoms, and Eating Problems) (Henkle, 2020). Each

domain score can range from 0 to 100 (with higher scores indicating better function). The recall period is 1 week, and each item uses a 4-point Likert scale.

7.5.5.4. St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease Patients

Patients will complete the SGRQ-C (Appendix F) at all study assessment time points specified in the Schedule of Assessments (Appendix A). The SGRQ-C is a measure to assess impaired health and perceived well-being (quality of life) (Jones, 1991). The SGRQ-C was designed to allow for comparative measurements of health and to quantify changes in health following treatment. Scores of 3 components (symptoms, activity, and impacts [on daily life]) and total score will be evaluated (Jones, 1992). Each subscale score ranges from 0 to 100 with a lower score indicating better quality of life. The recall period and verbal response scales vary between items.

7.5.5.5. Global Assessment Scales

7.5.5.5.1. Patient Global Impression of Severity

Patients will be asked to rate their overall severity of symptoms in the PGIS (Appendix G) at all study assessment time points specified in the Schedule of Assessments (Appendix A). Patients will be asked to choose the response that best describes the severity of the NTM lung disease symptoms over the past 7 days. The PGIS uses a 5-point Likert scale (None [0], Mild [1], Moderate [2], Severe [3], and Very Severe [4]) (Yalcin, 2003) (FDA, 2018).

7.5.5.5.2. Patient Global Impression of Change

Patients will be asked to rate the overall change in symptoms in the PGIC (Appendix G) at all study assessment time points specified in the Schedule of Assessments (Appendix A). Patients will be asked to choose the response that best describes the overall change in the severity of the NTM lung disease symptoms since starting the study. The PGIC uses a 5-point Likert scale (Much Better [0], A Little Better [1], No Change [2], A Little Worse [3], or Much Worse [4]) (Yalcin, 2003; FDA, 2018).

7.5.5.5.3. Clinician Global Impression of Severity

Investigators will be asked to rate their impression of the overall severity of the patient's symptoms in the CGIS (Appendix G) at all study assessment time points specified in the Schedule of Assessments (Appendix A). The Investigators will be asked to choose the response that best describes the severity of the patient's NTM lung disease symptoms (Busner, 2007). The CGIS uses responses of None (0), Mild (1), Moderate (2), Severe (3), or Very Severe (4).

7.5.5.5.4. Clinician Global Impression of Change

Investigators will be asked to rate their impression of the overall change in symptoms in the CGIC (Appendix G) at all study assessment time points specified in the Schedule of Assessments (Appendix A). Investigators will be asked to choose the response that best describes the severity of the patient's NTM lung disease symptoms compared to the baseline (Busner, 2007). The CGIC uses responses of Much Better (0), A Little Better (1), No Change (2), A Little Worse (3), or Much Worse (4).

7.5.5.6. Meaningful Change Question

After every time the PGIC is completed, the patient will answer a question to gauge whether the change (better, worse, same) in their symptoms is meaningful to them (Appendix H).

7.5.6. Qualitative Embedded Interviews

A subset of up to 40 patients in the Phase 2 part of the study will participate in an optional qualitative embedded interview to share their experience in the study. The final sample size will depend on site recruitment totals and participant willingness to complete the optional interview.

Patients who are enrolled in the Phase 2 part of the study must meet the following criteria to be considered eligible to participate in an interview:

- Complete their Month 6 Visit or receive at least 8 weeks of treatment if study drug was prematurely discontinued prior to Month 6.
- Be able to speak, read, and understand English or other approved language well enough (based on site staff judgment) to complete an interview via telephone or web conference and be willing to have their interview audio recorded.
- Not have issues with cognition or hearing, or other issues that would make it difficult (based on site staff judgment) to participate in an interview via telephone or web conference.

Evidera, a CRO, has been contracted to conduct the interviews. A site staff member will share patient contact information with Evidera via a secure location. Evidera staff will contact participants directly to schedule and conduct the interviews. All interviews will be conducted via telephone or web-based teleconference, based on participant preference and capabilities. Interviews will be conducted in English or other approved language and will last approximately 30 to 45 minutes. The interview will take place within 2 weeks (up to 4 weeks maximum) after the Month 6 Visit or within 1 week (up to 3 weeks maximum) after the EOT Visit (if the EOT Visit occurs within the first 6 months and if the patient has completed at least 8 weeks of treatment).

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. Interviewers will use an open-ended, semi-structured interview guide to lead the discussion. All interviews will be audio-recorded and transcribed for analyses.

It is possible that Phase 2 patients will report AEs during the course of their qualitative embedded interview. All Evidera researchers conducting interviews will undergo training to listen for suspected AEs. The Evidera researchers will not evaluate the suspected AE but rather will document the patient's report and alert the site study team within 24 hours for further evaluation, per study procedures.

Interviews will qualitatively evaluate the proposed symptom-based clinical response definition within the context of the clinical study. 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.

7.6. Randomization

Patients will be randomized using an IRT system per Sections 5.3 and 5.5.2.1.

7.7. Study Drug Administration

Study drug will be administered per Section 5.5.2.

7.8. Adverse Events Assessment

AEs will be assessed per Section 7.9.

7.9. Safety Monitoring and Reporting

See Section 7.5 and Appendix A for assessments and procedures related to safety, including vital signs, laboratory tests (eg, chemistry, hematology, urinalysis), ECGs, and AEs.

7.9.1. Adverse Events

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 a drug whether or not related to the drug.

All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded in the appropriate eCRF. AEs will be collected from the time of the first dose of study drug through EOT.

SAEs will be collected from the time of informed consent through LFU.

Any medical condition or signs/symptoms already present at the time of first dose of study drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs/symptoms present at baseline changes in severity, frequency, or seriousness at any time after administration of the first dose of study drug. In this case, it should be reported as an AE.

Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning with the date of the first dose of study drug, Investigators should make an assessment for AEs at each visit and record the event in the appropriate AE eCRF. If an observed or reported sign or symptom is part of the symptom-based clinical endpoint (eg, a worsening symptom associated with the underlying MAC lung infection), it should *not* be captured as an AE, with the exception of events that meet criteria for SAE (eg, deaths, hospitalizations); see Section 7.9.2.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded in the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE in the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at the time of first dose of study drug and significantly worsen during the study should be reported as TEAEs, if they cannot be ascribed to a specific medical condition or are associated with a specific underlying disease (eg, isolated elevation of ALT or AST that is not associated with a clear diagnosis or specific hepatic condition). Otherwise, abnormal laboratory values should be captured collectively under a unified disease or diagnosis (ie, a single TEAE disease term), rather than separate TEAEs for each individual laboratory abnormality. Clinically significant laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) include, but are not limited to, events that require intervention or if an action is taken with the study drug as a result of the abnormality. Abnormal test results that are determined to be an error should not be reported as an AE. The Investigator will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

All clinically significant abnormal laboratory values occurring during the clinical study must be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Such laboratory values will be captured as unscheduled assessments in the electronic data capture (EDC) system if they are collected outside of protocol-defined study visits (eg, after LFU).

7.9.1.1. Assessment of Adverse Events by the Investigator

7.9.1.1.1. Assessment of Severity

Investigators should use CTCAE version 5.0 (NIH, 2017) for guidance in determining the severity of TEAEs. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to AE

7.9.1.1.2. Causality Assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

- Definitely related: A reaction that follows a reasonable temporal sequence from administration of study drug, follows a known or expected response pattern to the study drug, disappears or decreases on cessation or reduction in study drug dose, and/or it reappears or worsens when the study drug is administered.

- Probably related: A reaction that follows a reasonable temporal sequence from administration of study drug, follows a known or expected response pattern to the study drug, and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.
- Possibly related: A reaction that follows a reasonable temporal sequence from administration of study drug and follows a known or expected response pattern to the study drug, but could have reasonably been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.
- Not related: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug. This definition implies there is not a reasonable possibility of a causal relationship between the event and the study drug, meaning that there are facts (ie, evidence) or arguments to suggest there is not a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug: The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug: The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

7.9.1.2. Adverse Events of Special Interest

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

For this study, GI intolerance and anemia are considered AESIs. During the course of the study, additional AESIs may be identified by the Sponsor.

Examples of AESIs related to GI intolerance include, but are not limited to: *C. difficile* colitis, Pseudomembranous colitis, *C. difficile* test positive, diarrhea, nausea, and vomiting.

Examples of 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, and RBC decreased.

7.9.2. Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

Events of progression of a patient's underlying disease including worsening signs/symptoms associated with the underlying MAC lung infection should not be reported as an SAE unless the outcome is fatal or requires hospitalization during the study or within the safety reporting period. If the event has a fatal outcome during that timeframe, the event must be recorded as an SAE with CTCAE Grade 5 (fatal) outcome indicated. Diagnosis of progression of disease alone should not be reported as an SAE.

SAEs will be reviewed by the Sponsor Medical Monitor and/or safety physician and further queries issued, if necessary. The ultimate determination of causality will be made in consideration of ICH and FDA guidelines.

7.9.3. Serious Adverse Event Reporting − Procedures for Investigators

7.9.3.1. Initial reports

All SAEs occurring from the time of informed consent through LFU must be reported to [redacted] Clinical Safety without undue delay but no later than within 24 hours of the knowledge of the occurrence. After LFU, any SAE that the Investigator considers related to study drug must be reported to the [redacted] Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] Safety at [redacted] or call the [redacted] SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to [redacted] (contact information listed in Section 7.9.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

7.9.3.2. Follow-up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.9.4. Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the Protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] Clinical Safety within 24 hours of knowledge of the event. [redacted] Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted] Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the Protocol, the Investigator should notify

[redacted] Clinical Safety as described above. The Investigator/site must make every effort to obtain a completed informed consent form (ICF) for the pregnant partner of a male patient.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to [redacted] Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

7.9.5. Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the countries and Member States concerned, and to the IECs, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned, and to the IECs concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to IMP.

Expedited reporting of SUSARs related to non-investigational medicinal products (NIMPs) (and any other NIMPs) is not required. Listings of cases related to NIMPs will be included in the Development Safety Update Report.

7.9.6. Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- Overdose: Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the Protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- Misuse: Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the Protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.

- Abuse: Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Medication error: Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of study drug are not considered reportable as medication error.
- Product complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to [redacted] Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded in the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: [redacted] Clinical Safety

[redacted] **SAE reporting line – United States and Canada:**
Telephone:
Fax:
Email:

[redacted] **SAE reporting line – Global:**
Telephone: +
Fax: +
Email:

8. STATISTICS

8.1. Analysis Populations

The following analysis populations will be defined in this study:

- Intent-to-Treat (ITT) Population: All patients who were randomized, regardless of whether they received any study drug
- Safety Population: Randomized patients who received any amount of study drug
- Micro-ITT Population: Patients who meet the definition for the ITT Population and have MAC culture-positive *Pre-Study* and *Screening* respiratory specimens (per Inclusion Criterion 3.a). Primary efficacy endpoint analyses in both Phase 2 and Phase 3 parts of the study will be performed in this patient population.
- Per-Protocol Population: Patients who meet the definition for the ITT Population and have no important protocol deviations that would affect the assessment of the primary efficacy outcome
- PK Population: All patients treated with at least 1 dose of epetraborole and who have at least 1 analyzable PK sample
- 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), Day 1, and at least Month 3 and/or Month 6 (for all other calculations).
- Embedded Interview Population (applicable to Phase 2 part only): Up to 40 Phase 2 patients who meet Micro-ITT Population and interview eligibility (per Section 7.5.6)

8.2. Statistical Methods

8.2.1. Analysis of Efficacy

Different primary and key secondary endpoints will be used for the purposes of review in the US and outside of the US, and full details of these analyses will be outlined in the SAP(s). The primary analysis population for the US and outside of the US will be the Micro-ITT Population.

Additional sensitivity analyses to address the impact of missing data due to COVID-19 may be added to the SAP.

8.2.1.1. Phase 2 Part of the Study

The Phase 2 part of the study will assess the performance of the $MACrO_2$ PRO, including responsiveness to change, with the aim of informing selection of the optimal PRO to be used in the Phase 3 part of the study. Psychometric analyses will aim to identify the most appropriate threshold to use within the target population for the individual $MACrO_2$ PRO items. This process will be outlined in the psychometric analysis plan. In summary, anchor-based approaches will be used to assess and confirm the proposed definition of clinical response (ie, improvement of

≥1 grade in the key symptom with no worsening of other symptoms for the $MACrO_2$ PRO). Empirical cumulative distribution function and probability density plots will also be examined. Distribution-based analyses will be used as supplemental evidence (FDA, 2019). Anchors will include other PRO measures (ie, the PGIS and PGIC) or clinical outcomes such as microbiological response. The results will be triangulated with the anchor-based analyses considered to be the primary evidence, distribution-based analyses treated as secondary evidence, and results from the embedded interviews to determine a single responder definition threshold or narrow ranges of values for the $MACrO_2$ PRO items.

In addition to the evaluation of the PROs, endpoints from the Phase 2 part of the study will undergo statistical analyses to estimate the effect of randomized treatment. The number and percentage of PRO symptom/function-based clinical responders and clinical non-responders will be presented by treatment group, as will the percentage of patients achieving a microbiological improvement or a microbiological sputum culture conversion. In each case, the response rate will be compared between treatment groups using the method of Miettinen and Nurminen. Statistical analysis of all endpoints for the Phase 2 part of the study will be described in the SAP(s).

After the last patient in Phase 2 completes the Month 6+1 week PRO assessment, prespecified members of the Sponsor and non-Sponsor analysis teams will be unblinded to treatment assignment for Phase 2 data analyses, but study staff conducting psychometric validation analyses will remain blinded. Patients, Investigators, and other study staff will also remain blinded to treatment assignment through LFU (see Study Blinding Plan). Prespecified members of the Sponsor and non-Sponsor analysis teams will review unblinded results from the Phase 2 analyses, based on data through Month 6, to verify the appropriate PRO measure and clinical response determinations for the superiority analysis in the Phase 3 part of the study. The current symptom-based clinical response definition (using the $MACrO_2$ PRO) in Phase 3 is a placeholder to be verified after Phase 2 analyses. Potential changes to clinical response criteria in the Phase 3 part of the study will be programmatical in nature and will not affect study conduct; regardless of the PRO or clinical responses determined for the Phase 3 primary analysis, patients in both the Phase 2 and Phase 3 parts of the study will complete the same set of PRO measures and microbiological assessments according to the Schedule of Assessments (Appendix A).

8.2.1.2. Phase 3 Part of the Study

The number and percentage of PRO symptom/function-based clinical responders and clinical non-responders will be presented by treatment group. Patients with missing data or incomplete PRO data at each relevant time point will be considered an indeterminate response and will be analyzed as a clinical non-responder. The clinical response rate will be compared between treatment groups using the method of Miettinen and Nurminen. Analyses of PRO symptom/function-based clinical responses will be conducted in the Micro-ITT and Per-Protocol populations.

The number and percentage of patients with microbiological responses by both decrease in MAC colony counts of ≥1 category and sputum culture conversion will be presented by treatment group. Microbiological responses will be compared between treatment groups using the method of Miettinen and Nurminen. Analyses of microbiological responses will be conducted in the Micro-ITT Population.

As there is 1 primary endpoint and 1 key secondary endpoint in each region (in the US or outside the US), a hierarchical testing approach will be applied, whereby the primary endpoint will be tested, and if superiority is concluded for the primary endpoint, the key secondary endpoint will then be tested. Note that, although the ordering of the primary endpoint and key secondary endpoint is reversed for the US and outside the US, the same approach to hierarchical testing will be used for the primary and key secondary endpoint appropriate for that region. As no specific claims are intended for other secondary endpoints, no further multiplicity testing will be applied for the other secondary and exploratory endpoints.

Analyses of the exploratory efficacy outcomes will be conducted to support the findings of the primary and secondary efficacy outcomes and will be described in the SAP(s).

8.2.2. Analysis of Safety

Safety will be evaluated for the Safety Population by presenting the summaries of TEAEs, clinical laboratory evaluations (chemistry, hematology, and urinalysis), vital signs, and 12-lead ECG parameters. A TEAE is defined as an AE that occurs during or after the first administration of study drug on Day 1 through the EOT Visit. All SAEs occurring from the time of informed consent through LFU will be collected.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v25.0 or later. An overall summary of AEs will be provided by treatment group. The incidence of TEAEs will be presented by SOC and PT; by SOC, PT, and relationship to study drug; and by SOC, PT, and maximum severity. SAEs and TEAEs that lead to premature discontinuation of study drug will also be presented by SOC and PT.

Descriptive statistics for clinical laboratory results, vital signs, and 12-lead ECG parameters, including change from baseline, will be presented by time point collected. Incidences of potentially clinically significant clinical laboratory results, vital signs, and 12-lead ECG parameters, as defined in the SAP(s), will also be summarized.

8.2.3. Analysis of Pharmacokinetics

Plasma PK will be analyzed for all patients treated with at least 1 dose of epetraborole and who have at least 1 analyzable PK sample. A population PK analysis will be performed to assess exposure and PK parameters of epetraborole. Plasma PK samples obtained from the epetraborole group will be analyzed using a validated assay by a central bioanalytical laboratory. Samples from placebo-treated patients will not be analyzed. Masked individual and composite plasma PK data from an initial group of patients in the Phase 2 part of the study will be reviewed by a PK Data Review Committee to assess epetraborole exposures (Section 8.3.1). 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 confirmation. The methods to be employed for this interim analysis will be presented in a data analysis plan and results reported in a separate PK report.

8.2.4. Sample Size Determination

8.2.4.1. Phase 2 Part of the Study

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 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 correlation coefficient of 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 5 response options). In addition, using assumed true response rates of 30% for the epetraborole arm and 10% for the placebo arm for either a PRO symptom-based clinical response (in the US) or a microbiological culture conversion response (outside the US), a Phase 2 evaluation in 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.

8.2.4.2. Phase 3 Part of the Study

No data are available on clinical symptom 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 revealed Month 6 sputum culture conversion rates of 29.0% compared with 8.9%, respectively (Griffith, 2018). 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 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 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 epetraborole and 78 placebo patients) 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 (Griffith, 2018) (see Inclusion Criterion 3.a); 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 through Month 6. Any needed sample size adjustment for Phase 3 will be determined as part of the review of unblinded Phase 2 data.

8.3. Data Committees

8.3.1. 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 exposure. 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 blinded 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.

8.3.2. 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, including vital signs, ECG findings, laboratory tests (eg, hematology, blood chemistry), AEs (including SAEs and AESIs), and any other relevant safety information, 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 recommendation 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 are available in the EBO-301 DSMB Charter.

8.4. Study Stopping Criteria

Individual patient stopping rules are outlined in Section 4.3, and criteria for premature discontinuation of study drug are provided in Section 4.4.

The study may be terminated or temporarily suspended by the Sponsor for any reason, including if suggested by the DSMB or a regulatory authority. Reasons for study termination or suspension may include but are not limited to, unanticipated safety signal or change in benefit/risk profile of the study drug detected during safety monitoring.

As described in Section 8.3.2, the independent DSMB established for the study will make recommendations to the Sponsor regarding continuation or termination of the study.

9. DATA MANAGEMENT AND RECORD KEEPING

9.1. Data Management

9.1.1. Data Handling

Data will be recorded at the site in eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

9.1.2. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

9.1.3. Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) and other appropriate international regulations. All passwords will be strictly confidential, user specific, and cannot be shared.

9.1.4. Medical Information Coding

For medical information, the following will be used:

- MedDRA v25.0 (March 2022 release) or later for medical history, concomitant procedures, and AEs
- World Health Organization Drug Dictionary (WHODrug Global B3; March 2022 release or later) for prior and concomitant medications

9.1.5. Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

9.2. Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study.

Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

9.3. End of Study

The end of the study ("study completion") is defined as the date of the last Protocol-specified visit/assessment (LFU Visit) for the last patient in the study.

10. INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

10.1. Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

10.2. Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The Protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the Protocol, any Protocol Amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site until written IRB/IEC authorization has been received by the Sponsor.

It is the responsibility of the Sponsor or their designee (ie, [redacted] to obtain the approval of the responsible IECs according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given and the Sponsor or their designee provides written approval that all requirements have been satisfied.

10.3. Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements, as set forth in the Clinical Study Agreement.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

10.4. Patient Card

For all sites, on enrollment in the study, the patient will receive a patient emergency card. The patient emergency card will state that the patient is participating in a clinical research study, type of treatment, number of treatments received, and contact details in case of an SAE.

10.5. Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the Protocol, IRB/EC regulations, ICH GCP, applicable regulatory requirements, all applicable local or regional regulations, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel all applicable study documents, procedures, and processes.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and Protocol adherence are satisfactory. During the monitoring visits, information recorded in the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the data are entered in the eCRFs by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

10.6. Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. A summary of the results of the study will be available within 1 year of the completion of the study unless a deferral is granted. Patients may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

The conduct of this study and the processing of any personal data collected from each subject (or from a subject's healthcare professional or other relevant third-party sources) by the Sponsor or it's designee, the site, and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations.

10.7. Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to

link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

10.8. Publication Policy

Data from this study may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

10.9. Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under Title 21 of CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

10.10. Insurance and Indemnity

For sites in the European Union, in accordance with the relevant national regulations, the Sponsor will obtain patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study’s execution.

10.11. Legal Aspects

For sites in the European Union, the clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorisation (CTA). The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

10.12. Clinical Study Report Signatures

The final clinical study report will be approved by the Sponsor and the overall Coordinating Investigator. The Coordinating Investigator will be chosen from the Principal Investigators who enroll patients in the study and are experts within the NTM community.

11. STUDY ADMINISTRATIVE INFORMATION

11.1. Protocol Amendments

Any amendments to the study Protocol will be communicated to the Investigators by [redacted] or the Sponsor. All Protocol Amendments will undergo the same review and approval process as the original Protocol. A Protocol Amendment may be implemented after it has been approved by the IRB/IEC unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

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APPENDIX A. SCHEDULES OF ASSESSMENTS

Table 3: Schedule of Assessments: Screening through Month 6 (Phases 2 and 3)

		Screening		Treatment Period								
	Month			Randomization	1[a]	2[a]	3[a]	3+1w	4[a]	5[a]	6[b]	6+1w
	Study Day/Visit Window[c]	D-56 to -15	D-14 to -7	D1	D29 ±7d	D57 ±7d	D85 ±7d	1w (+1d) after M3	D113 ±7d	D141 ±7d	D169 ±7d	1w (+1d) after M6
	Informed consent[d]	X										
	Inclusion/exclusion criteria	X[e]										
	Demographic information	X										
	Medical/surgical history	X	X	X								
Tests/Exams	Physical examination[f]	X		X	X	X	X		X	X	X	
Tests/Exams	Vital signs, weight[g]	X		X	X	X	X		X	X	X	
Tests/Exams	Height, BMI[g]	X										
Tests/Exams	12-lead ECG[h]	X		X		X			X		X	
Tests/Exams	Chest CT (non-contrast)[i]	X									X	
Laboratory	Chemistry/Hematology[j]	X[e]		X[k]	X	X	X		X	X	X	
Laboratory	Urinalysis[h]	X		X[k]		X			X		X	
Laboratory	Serum pregnancy test (FOCP only)[h]	X		X[k]								
Laboratory	CrCl calculation[l]	X										
Laboratory	ADH genotyping[m]			X								
Laboratory	Sputum collection[n]	X			X	X	X		X	X	X	
Laboratory	Plasma PK sampling[o]			X	X							
PROs	$MACrO_2$ PRO[p,q]		X[r]	X[s]	Weekly			X[s]	Weekly			X[t]
PROs	QOL-B, NTM Module, SGRQ-C[p]		X[s]	X[s]	X	X	X		X	X	X	
PROs	PGIS[p]		X[s]	X[s]	X	X	X	X[t]	X	X	X	X[t]
PROs	PGIC[p]				X	X	X		X	X	X	
PROs	Meaningful Change Question[t]				X	X	X		X	X	X	
PROs	CGIS[u]			X	X	X	X		X	X	X	
PROs	CGIC[u]				X	X	X		X	X	X	
	Qualitative Embedded Interview										X[v]	
	Randomization			X								
	OBR administration[w]	X	X	X								
	Study drug administration			Daily[x]								
	Prior/concomitant medications	X	X	X	X	X	X		X	X	X	
	Adverse events[y]	X	X	X	X	X	X		X	X	X	

Note: See Table 4 for Months 7-16, EOT/ET, and LFU assessments.
Abbreviations: ADH = alcohol dehydrogenase; AE = adverse event; BMI = body mass index; CGIC = Clinician Global Impression of Change; CGIS = Clinician Global Impression of Severity; CrCl = creatinine clearance; CT = computed tomography; D = Day; ECG = electrocardiogram; EOT = End of Therapy; ET = Early Termination; FOCP = female of childbearing potential; HHC = home health care; LLN = lower limit of normal; MAC = *Mycobacterium avium* complex; NTM = Nontuberculous mycobacteria; OBR = optimized background regimen; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); PRO = Patient-Reported Outcome; QD = once daily; QOL-B = Quality of Life-Bronchiectasis; SAE = serious adverse event; SGRQ-C = St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease patients; TEAE = treatment-emergent adverse event; w = week.

[a] Visit may be conducted in person or via HHC, if available.
[b] All reasonable efforts should be made to conduct Month 6 and EOT visits in person but HHC will be supported, if needed.
[c] Study days are anchored to Day 1.
[d] Signed informed consent: Must obtain before any study-related procedures are performed.
[e] Laboratory tests required for eligibility are listed in Section 7.5.2. For eligibility purposes, clinical laboratory tests may be repeated once if an abnormal result is observed at the initial reading during Screening.
[f] Physical Exam: See Section 7.5.1.1; perform before the administration of study drug at the treatment visits.
[g] Vital Signs, Height (without shoes), Weight, BMI: See Section 7.5.1.2; when possible, obtain vitals after at least 5 minutes resting in a supine or sitting position. For eligibility purposes, vital signs may be repeated once if an abnormal result is observed at the initial reading during Screening.
[h] ECGs: See Section 7.5.1.3 for details, including timing of Screening triplicate ECGs and single ECGs thereafter. Collect ECGs after at least 5 minutes resting in a supine or semi-recumbent position. *[In Japan:]* See Section 7.5.1.3 for timing ECGs for patients in Japan. For eligibility purposes, ECGs may be repeated once if an abnormal result is observed at the initial reading during Screening.
[i] Chest CTs: See Section 7.5.1.4 for details, including timing of chest CTs for eligibility.
[j] Laboratory samples (central laboratory): See details in Section 7.5.2 and list of analytes in Appendix B. For patients with an initial Screening hemoglobin of ≥10.0 g/dL to <LLN or ≥6.2 mmol/L to <LLN, retest hemoglobin at the central clinical laboratory (results must be available prior to randomization).
[k] Laboratory samples: On Day 1, collect prior to first dose of study drug.
[l] CrCl Calculation: Use the Cockcroft-Gault formula and serum creatinine levels obtained at the central laboratory prior to Day 1 and as needed throughout the study per routine standard of care. Calculate estimated CrCl every time a local laboratory assessment of serum creatinine is performed (Section 5.5.2.3).
[m] ADH genotyping: Genetic variants will be tested to determine effects on PK analysis results; the results are not needed prior to dosing and will not impact study eligibility.
[n] Sputum Samples (regional or central microbiological laboratory): See details in Section 7.5.3; collect 2 to 3 sputum samples at each time point; samples may be collected on the same day or within a 5-day window beginning with collection of the first sample.
[o] Plasma PK Sampling (central bioanalytical laboratory): Collect PK blood samples from all patients in a blinded and fasting manner per Section 7.5.4 and Table 2. If a patient is unable to complete either or both of the scheduled Day 29 PK blood draws, these samples may be obtained at a subsequent visit as unscheduled PK samples. Preferably, both Samples 2 and 3 will be obtained on the same day. In circumstances when *either* Sample 2 or Sample 3 (but not both) were previously collected, the missing sample alone may be collected at a subsequent visit. The date and time of each unscheduled blood draw should be recorded in the EDC system along with the estimated date and time of the last dose of study drug taken before the PK sample.
[p] PRO to be completed by patient; see details in Section 7.5.5.
[q] $MACrO_2$: See Section 7.5.5.1 and Appendix C; during the Treatment Period, complete once weekly for the first 6 months (including Month 3 + 1 week and Month 6 + 1 week for test-retest reliability; and at monthly clinic visits). Item 8 will be completed at the first 2 predose time points and not thereafter
[r] PRO to be completed twice before the first dose of study drug, and will serve as the baseline assessment for comparison to on-treatment assessments.
[s] For patients whose EOT Visit coincides with the Month 3 or Month 6 visit, the MACrO2, and PGIS will be completed 1 week (+1 day) after the EOT Visit.
[t] Meaningful Change Question: See Section 7.5.5.6 and Appendix H; question to be answered after each completion of the PGIC.
[u] PRO to be completed by Investigator or designee; see details in Section 7.5.5.

[v] Qualitative Embedded Interview: See Section 7.5.6. A subset of eligible patients in the Phase 2 part of the study will participate in a telephone or web conference interview within 2 weeks (up to 4 weeks maximum) after the Month 6 Visit or within 1 week (up to 3 weeks maximum) after the EOT Visit if the EOT Visit occurs within the first 6 months and if the patient received at least 8 weeks of treatment.

[w] OBR Administration: See Section 5.7. For patients whose OBR was stopped prior to Screening, an OBR consisting of ≥2 agents from their most recent regimen must be restarted at Screening.

[x] Study Drug Administration: See Section 5.5.2; tablets to be administered QD in a fasting state (no food for at least 1 hour before and at least 2 hours after study drug administration). The first dose of study drug will be administered in the presence of the Investigator or designee following randomization.

[y] AE Collection: See Section 7.9 for details on collection, monitoring, and reporting of TEAEs, including SAEs.

Table 4: Schedule of Assessments: Months 7-16, EOT, and LFU (Phases 2 and 3)

		Treatment Period[a]								
	Month	7, 8[b]	9[b]	10, 11[b]	12[b]	13, 14[b]	15[b]	16[b]	EOT Visit/ET[c]	LFU Visit[d]
	Study Day/Visit Window[e]	D197, 225 ±7d	D253 ±7d	D281, 309 ±7d	D337 ±7d	D365, 393 ±7d	D421 ±7d	D449 ±7d		
Tests/Exams	Physical examination[f]		X		X		X		X	X
	Vital signs[g]	X	X	X	X	X	X	X	X	X
	Weight		X		X		X		X	X
	12-lead ECG[h]								X	
	Chest CT[i]								X	
Laboratory	Chemistry/Hematology[j]	X	X	X	X	X	X	X	X	X
	Urinalysis[j]		X		X		X		X	X
	Serum pregnancy test (FOCP only)[j]								X	
	Sputum collection[k]		X		X		X		X	X
PROs	$MACrO_2$ PRO[l]		X		X		X		X[m]	X
	QOL-B, NTM Module, SGRQ-C[l]		X		X		X		X	X
	PGIS, PGIC[l]		X		X		X		X[m]	X
	Meaningful Change Question[n]		X		X		X		X	X
	CGIS, CGIC[o]		X		X		X		X	X
	Qualitative Embedded Interview								X[p]	
	OBR administration	X[a, q]								
	Study drug administration	Daily[a, r]								
	Prior/concomitant medications	X	X	X	X	X	X	X	X	X
	Adverse events[s]	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; CGIC = Clinician Global Impression of Change; CGIS = Clinician Global Impression of Severity; CT = computed tomography; D = Day; ECG = electrocardiogram; EOT = End of Therapy; ET = Early Termination; FOCP = female of childbearing potential; HHC = home health care; LFU = Late Follow-up; MAC = *Mycobacterium avium* complex; NTM = Nontuberculous mycobacteria; OBR = optimized background regimen; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = Patient-Reported Outcome; QD = once daily; QOL-B = Quality of Life-Bronchiectasis; SAE = serious adverse event; SGRQ-C = St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease patients; TEAE = treatment-emergent adverse event.

[a] Each patient's duration of treatment will vary depending on the timing of their MAC culture conversion; see Section 3.1.1 for details.

[b] Visit may be conducted in person or via HHC, if available.

[c] EOT Visit/ET: Perform EOT Visit within 7 calendar days after the last dose of study drug. All reasonable efforts should be made to conduct EOT Visit in person but HHC will be supported, if needed. The EOT assessments may be performed during a regularly scheduled clinic visit if within the EOT window. Patients with clinically significant abnormal laboratory values at EOT that are deemed possibly or probably related to study drug will have repeated laboratory assessments until values return to normal or pre-study baseline values. For patients who are withdrawn from the study prior to completion, all the EOT Visit procedures will be performed at an ET Visit.

[d] LFU Visit: Perform 3 months (84 days ±14 days) after the last dose of study drug. Visit may be conducted in person or via HHC, if available.

[e] Study days are anchored to Day 1.
[f] Physical Exam: See Section 7.5.1.1; perform before the administration of study drug at the treatment visits.
[g] Vital Signs: See Section 7.5.1.2; when possible, obtain vitals after at least 5 minutes resting in a supine or sitting position.
[h] ECGs: See Section 7.5.1.3; when possible, collect ECGs after at least 5 minutes resting in a supine or semi-recumbent position.
[i] Chest CTs: See Section 7.5.1.4 for details, including timing of EOT CTs.
[j] Laboratory samples (central laboratory): See details in Section 7.5.2 and list of analytes in Appendix B.
[k] Sputum Samples (regional or central microbiological laboratory): See details in Section 7.5.3 including instructions for sputum collection at home; collect 2 to 3 sputum samples at each time point; samples may be collected on the same day or within a 5-day window beginning with collection of the first sample.
[l] PRO to be completed by patient; see details in Section 7.5.5.
[m] For patients whose EOT Visit coincides with the Month 3 or Month 6 visit, the $MACrO_2$, and PGIS will be completed 1 week (+1 day) after the EOT Visit.
[n] Meaningful Change Question: See Section 7.5.5.6; question to be answered after each completion of the PGIC.
[o] PRO to be completed by Investigator or designee; see details in Section 7.5.5.
[p] Qualitative Embedded Interview: See Section 7.5.6. A subset of eligible patients in the Phase 2 part of the study will participate in a telephone or web conference interview within 1 week (up to 3 weeks maximum) after the EOT Visit if the EOT Visit occurs within the first 6 months and if the patient received at least 8 weeks of treatment.
[q] OBR Administration: See Section 5.7.
[r] Study Drug Administration: See Section 5.5.2; tablets to be administered QD in a fasting state (no food for at least 1 hour before and at least 2 hours after study drug administration).
[s] AE Collection: See Section 7.9 for details on collection, monitoring, and reporting of TEAEs, including SAEs.

APPENDIX B. CLINICAL LABORATORY ANALYTES

Hematology	Serum Chemistry	Urinalysis
Red blood cell (RBC) count	Liver Tests:	pH
Red cell distribution width	• Albumin	Specific gravity
Reticulocyte count (% and absolute)	• Alkaline phosphatase (ALP)	Bilirubin
White blood cell (WBC) count and differential[a]	• Alanine transaminase (ALT)	Blood
Hemoglobin (HGB)	• Aspartate transaminase (AST)	Glucose
Hematocrit	• Bilirubin direct	Ketones
Platelet count	• Bilirubin, indirect	Leukocyte esterase
Mean corpuscular volume	• Bilirubin, total	Microscopy[c]
Mean corpuscular HGB	• Gamma-glutamyl transferase (GGT)	Nitrite
Mean corpuscular HGB concentration	Amylase	Protein
Mean platelet volume	Anion gap	Urobilinogen
	Bicarbonate	**Other**
	Adjusted calcium	• Serum β-human chorionic gonadotropin (FOCP only)
	Blood urea nitrogen (BUN) or urea	• Alcohol dehydrogenase (ADH) genotyping
	Calcium	
	Chloride	
	Cholesterol	
	Creatine kinase	
	Creatinine	
	Creatinine clearance (calculated using Cockcroft-Gault formula)[b]	
	Erythropoietin levels	
	Folate	
	Globulin	
	Glucose	
	Iron Studies:	
	• Iron	
	• Transferrin	
	• Transferrin saturation	
	• Ferritin	
	Lactate dehydrogenase	
	Phosphorus, inorganic	
	Potassium	
	Protein, total	
	Sodium	
	Uric Acid	
	Vitamin B12	

Notes: Laboratory evaluations required to confirm eligibility are listed in Section 7.5.2. Clinical laboratory samples for eligibility and clinical safety evaluations will be analyzed by a certified central clinical laboratory.
Abbreviation: FOCP = female of childbearing potential.

[a] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range. Neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be reported as absolute and percent.

[b] Estimated CrCl (mL/min) = (140 − Age [years]) × Actual Body Weight [kg] × [0.85 if Female]) / (72 × Serum Creatinine [mg/dL]).

[c] Microscopy is performed only as needed based on positive dipstick test results.