Clinical Trial Protocol: PTK0796-NTM-20203

Study Title:	A Phase 2, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Omadacycline in Adult Subjects with Nontuberculous Mycobacterial (NTM) Pulmonary Disease Caused by *Mycobacterium abscessus* Complex (MABc)
Study Number:	PTK0796-NTM-20203
Study Phase:	2
Product Name:	Omadacycline (PTK 0796)
IND Number:	75,928 73,431
Indication:	Nontuberculous Mycobacterial (NTM) Pulmonary Disease Caused by *Mycobacterium abscessus* Complex (MABc)
Investigators:	Multicenter
Sponsor:	Paratek Pharmaceuticals, Inc. 1000 First Ave Suite 200 King of Prussia, PA 19406 75 Park Plaza, 3rd Floor Boston, MA 02116
Sponsor Contact:	Telephone: +1 617-275-0040
Global Medical Monitor	[redacted], MD

Protocol Version 2.0:	06-December-2021
Original Protocol Version 1.0:	16-March-2021

Confidentiality Statement

SYNOPSIS

Sponsor:
Paratek Pharmaceuticals, Inc.

Name of Finished Product:
Omadacycline tablet, 150 mg

Name of Active Ingredient:
Omadacycline tosylate

Study Title:
A Phase 2, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Omadacycline in Adult Subjects with Nontuberculous Mycobacterial (NTM) Pulmonary Disease Caused by *Mycobacterium abscessus* Complex (MABc)

Study Number:
PTK0796-NTM-20203

Study Phase: 2

Study Rationale:
Omadacycline is an aminomethylcycline, a tetracycline class antibiotic, for intravenous or oral administration. Intravenous NUZYRA® (omadacycline) and oral NUZYRA tablets have been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections caused by susceptible microorganisms.

More than 140 nontuberculous mycobacterial (NTM) species have been identified, with more than half of the NTM pulmonary infections in the US associated with *Mycobacterium avium* complex (MAC) (Prevots 2010; Spaulding 2017). *Mycobacterium abscessus* complex (MABc) is the second most common NTM grouping causing human disease in the US, comprising about 10% of all NTM pulmonary infections across various study sites (Prevots 2015). In 2010, the number of national cases of NTM pulmonary infections was estimated as 86,244 (Strollo 2015). More recently in 2019, the number of NTM pulmonary cases was estimated to be as high as 115,000 nationally (Insmed Presentation 2021). The annual prevalence of NTM pulmonary infections in the US in 2015 was estimated as 11.7 per 100,000, representing a 7.5% annual increase from 2008 (Winthrop 2020).

Infections caused by MABc are notoriously difficult to treat due to intrinsic resistance to many classes of antibiotics. Few oral antibiotics demonstrate in vitro activity against MABc, making long-term treatment extremely difficult. Currently there are no FDA-approved treatments for pulmonary disease caused by MABc. Current treatment options (off-label treatments) are typically lengthy and require complex, multi-drug

regimens (Strnad 2018). Most of the antibiotics recommended for the treatment of MABc have safety and tolerability profiles that are not conducive to an extended treatment course. Therefore, a clear unmet need exists for an effective antibiotic with a favorable safety and tolerability profile which can be administered orally. Omadacycline has the potential to fill this unmet need.

Please refer to the current version of the Investigator's Brochure for additional information on omadacycline.

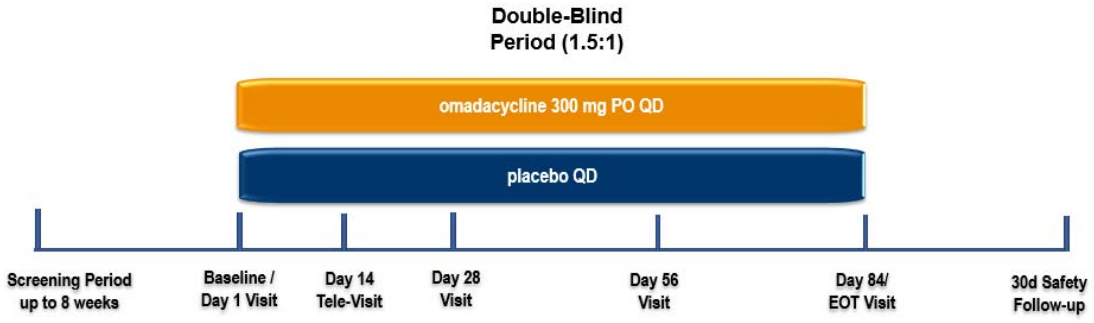
Objectives and Endpoints:

Objective	Endpoint
Primary	
Efficacy: To evaluate the efficacy of omadacycline in adult subjects with Nontuberculous Mycobacterial (NTM) pulmonary disease caused by *Mycobacterium abscessus* complex (MABc) based upon subject assessment of symptoms	Including but not limited to: • Clinical response at Day 84 defined as improvement in severity of at least 50% of the symptoms present at baseline • Clinical response at Day 84 defined as improvement in severity of at least 50% of the symptoms present at baseline and no deterioration in severity of symptoms present at baseline
Safety: To evaluate the safety and tolerability of omadacycline in adult subjects with NTM pulmonary disease caused by MABc	• Incidence of adverse events (AEs) and serious adverse events (SAEs) • Change from baseline for: o Clinical laboratory parameters o Vital signs o Electrocardiograms (ECGs) • Incidence of potentially clinically significant: o Clinical laboratory parameters o Vital signs o ECGs
Secondary	
To evaluate patient-reported outcomes and quality of life in adult subjects with NTM pulmonary disease caused by MABc	• Quality of Life – Bronchiectasis (QOL-B) • St. Georges Respiratory Questionnaire (SGRQ) • Patient-Reported Outcomes Measurement Information System Short Form v1.0 – Fatigue 7a Daily

	(PROMIS Short Form v1.0 – Fatigue 7a Daily) • Patient Global Impression of Change (PGI-C) • Patient Global Impression of Severity (PGI-S) • Clinical Global Impression – Severity of Illness (CGI-S) • Clinical Global Impression – Global Improvement Scale (CGI-I) • No new symptom (ie, symptom not present at baseline) with severity worse than mild
To evaluate the microbiological response of omadacycline in adult subjects with NTM pulmonary disease caused by MABc	• Decrease in quantitative sputum culture at Day 84 • Time to growth in liquid medium only • Time to first negative sputum culture

Study Design:

This is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multi-center study in adults with NTM pulmonary disease caused by MABc.



Following a Screening period of up to 56 days (8 weeks) prior to dosing, eligible subjects will be randomized (1.5:1) to receive either 300 mg once daily oral omadacycline monotherapy or matching placebo.

Subjects will attend monthly visits during the approximately 84 day (3-month) double-blind treatment period and will complete a 14-day safety tele-visit as well as a safety follow-up call approximately 30 days after their last dose of test article.

Approximate Duration of the Study:

Following an estimated recruitment period of approximately 24 months, the total duration of subject participation in the study is approximately 5 months which includes a total duration of study treatment for approximately 3 months (84 days).

Study Population:

Approximately 75 subjects (45 omadacycline and 30 placebo) will be enrolled at up to 20 sites. Subjects will be randomized (1.5:1) to receive either omadacycline or placebo. Subjects will be stratified according to their use of prior antibiotics for treatment of MABc NTM infection (received prior treatment vs. no prior treatment).

Main Criteria for Inclusion:

Subjects must meet all of the following criteria at Screening and/or Baseline to be eligible to participate in the study:

1. Written and signed informed consent must be obtained before any protocol-specific assessment is performed.
2. Male and female subjects age 18 years or older.
3. Diagnosed MABc pulmonary disease as per Infectious Diseases Society of America/American Thoracic Society guidelines criteria. Subjects must have:
    - At least 2 of the following NTM-infection symptoms at Screening and Baseline:
        - Chronic cough, coughing up blood (hemoptysis), wheezing, chest pain, frequent throat clearing, phlegm or sputum production, shortness of breath, fatigue, fever, night sweats, poor appetite, and/or weight loss.
    - At least 1 positive pulmonary culture for MABc in the 6 months prior to Screening, and 1 positive culture at Screening (note: prior culture and screening cultures must be at least 30 days apart).
    - Radiographic evidence of MABc infection via computed tomography (CT) scan of the chest within 3 months prior to Screening with findings consistent with NTM pulmonary disease. If no CT scan obtained within previous 3 months, one should be performed at Screening to confirm eligibility.
4. Based on the clinical assessment of the investigator, guideline-directed antibiotic therapy for treatment of MABc will not be required within the next 3 months, and a delay, in order for the subject to participate in a placebo-controlled clinical trial, is considered reasonable and clinically acceptable.
5. Be able to produce approximately 5 mL of sputum via spontaneous expectoration or be willing to undergo sputum induction to produce approximately 5 mL of sputum for microbiological evaluation.
6. Females must have a negative serum pregnancy test and agree to use a highly effective form of birth control (eg, abstinence, oral contraceptive, intrauterine device, or barrier contraception [eg, condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through study completion.

Males (if sexually active) must agree to use a highly effective method of birth control with female partner(s) from Screening through study completion.

7. Able and willing to adhere with the requirements and restrictions of the study.

Main Criteria for Exclusion:

Subjects meeting any of the following criteria at Screening and/or Pre-dose will be excluded from participation in the study:

1. Pregnant or nursing (breastfeeding) women.
2. Has received antibiotic treatment within 6 months prior to Screening for MABc or MAC.
3. Has received systemic or inhaled antibiotic therapy (other than chronic macrolide therapy) within 4 weeks prior to Screening.
4. Is experiencing an exacerbation of an infection with a non-*Mycobacterium* species (eg, *Pseudomonas aeruginosa*) that the investigator considers clinically relevant.
5. Has any of the following medical conditions:
   - Active pulmonary malignancy (primary or metastatic), or any type of malignancy requiring chemotherapy or radiation within 1 year prior to Screening.
   - Active allergic bronchopulmonary mycosis, or any other condition requiring chronic treatment with systemic corticosteroids (ie, prednisone dose ≥ 15 mg/day for a period of ≥ 4 consecutive weeks above this level) within 90 days prior to Screening.
   - Radiologic evidence of cavitary disease.
   - Known active pulmonary tuberculosis.
   - Cystic fibrosis.
   - History of lung transplantation.
   - Another advanced lung disease with a known percent predicted forced expiratory volume in 1 second < 30%.
   - Disseminated, extra-pulmonary NTM disease.
6. Screening calculated creatinine clearance < 30 mL/minute, using the Cockcroft-Gault equation, requirement for any form of dialysis (eg, hemodialysis, peritoneal dialysis), or other evidence of severe renal disease.
7. Has any of the following at Screening:
   - Alanine aminotransferase or aspartate aminotransferase ≥ 3 × upper limit of normal.
   - Total bilirubin > 1.5 × upper limit of normal.
   - Suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy).
8. History of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening.

9. Significant immunological disease determined by any of the following:
   - Current or anticipated neutropenia defined as < 500 neutrophils/mm^3.
   - Known infection with human immunodeficiency virus (HIV).
10. History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline, tigecycline, or omadacycline).
11. Has been previously treated with omadacycline.
12. History of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
13. Systemic treatment with disease-modifying antirheumatic agents, corticosteroids (equivalent to prednisone dose ≥ 15 mg/day for a period of ≥ 4 consecutive weeks above this level) or immunosuppressive agents in the 90 days prior to Screening.
14. Has current evidence of active pancreatitis.
15. Evidence or history of any other clinically significant medical condition or planned medical intervention that may, in the opinion of the investigator, pose a significant safety risk, impair study participation, impact the subject's ability to undergo the required study procedures or ability to complete the expected course of study treatment.
16. Any surgical or medical condition that, in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism, or excretion of drugs.
17. Inability to fast for 4 hours prior to dosing and/or 2 hours after dosing.
18. Per discretion of the investigator, subject is not expected to survive the duration of the study.

Test Article, Dose, and Mode of Administration:

- 300 mg oral omadacycline (2 × 150 mg tablets administered once daily, q24h)
- Placebo tablets resembling omadacycline (2 tablets administered once daily, q24h)

All doses should be taken in a fasted state. Fasting is defined as no food, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc), or drink except water for at least 4 hours before dosing. After dosing, no food or drink (except water) is permitted for 2 hours and no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

Duration of Treatment:

The total duration of blinded treatment is approximately 3 months (84 days).

Efficacy Assessments:

- Subject-reported NTM-pulmonary infection symptoms using a 4-point scale (absent, mild, moderate, severe)
- Quantitative sputum culture
- Patient-reported outcomes and quality of life measures:
  - QOL-B
  - SGRQ
  - PROMIS Short Form v1.0 – Fatigue 7a Daily
  - PGI-C
  - PGI-S
  - CGI-S
  - CGI-I

Safety Assessments:

Safety and tolerability will be assessed by monitoring the following:

- AEs and SAEs
- Physical examinations
- Vital signs (body weight, body temperature, blood pressure, heart rate)
- Laboratory tests (hematology and serum chemistry)
- ECGs
- CT scan

Pharmacokinetic Assessments:

Not applicable.

STATISTICAL METHODS:

A Statistical Analysis Plan (SAP) will be prepared and finalized before database lock and analyses of data. Summary data will be tabulated and presented by treatment group.

Sample Size Determination:

As the study is exploratory with respect to determination of efficacy, the sample size determination is provided to better ensure sufficient subjects are enrolled to provide an initial assessment of efficacy rather than test a specific hypothesis. With a randomization ratio of 1.5:1, a sample size of 75 subjects (45 omadacycline and 30 placebo) will provide approximately 80% power to detect an absolute treatment difference of 30% in clinical response rate at Day 84, based on clinical response rates of 15% and 45% in the placebo and omadacycline treatment groups respectively, using a Mantel-Haenszel test with 2-sided alpha level of 0.05.

Analysis Sets:

The following subject analysis sets have been defined:

- Intent-to-treat (ITT) Analysis Set includes all randomized subjects.
- Per-Protocol Analysis Set includes all randomized subjects who received at least 1 dose of test article and completed the study without major protocol deviations that affect the assessment of efficacy.
- Safety Analysis Set includes all subjects who received at least 1 dose of test article.

Safety Assessments:

All safety data will be analyzed in the Safety Analysis Set. Adverse events will be coded using the Medical Dictionary of Regulatory Activities. The incidence of treatment-emergent adverse events will be presented by system organ class (SOC) and preferred term (PT); by SOC, PT, and relationship to test article; and by SOC, PT, and severity. Serious AEs and treatment-emergent adverse events that lead to discontinuation of the test article will also be presented by SOC and PT. Descriptive statistics for clinical laboratory test results, vital signs, and ECG parameters, including change from baseline, will be presented by timepoint collected and for the overall most abnormal post-baseline value (for clinical laboratory results and vital signs). Incidences of potentially clinically significant clinical laboratory results, vital signs, and ECG parameters, as defined in the SAP, will also be summarized by timepoint collected and the overall most abnormal post-baseline value (for clinical laboratory results and vital signs).

Efficacy Assessments:

The study is exploratory with respect to efficacy determination. Efficacy will be evaluated based on endpoints defined by subject-reported NTM symptoms, subject-reported outcomes and quality of life measures, and microbiologic assessment. Additional endpoints to assess efficacy will be defined in the SAP. Nominal p-values are provided as descriptive statistics.

Clinical response at Day 84 will be defined as (1) improvement in severity of at least 50% of symptoms present at baseline and (2) improvement in severity of at least 50% of symptoms present at baseline and no deterioration in severity of symptoms present at baseline. Subjects who receive alternative antibiotic therapy for treatment of the NTM infection, withdraw consent, and/or die before reaching Day 84 will be considered as not achieving clinical response. For both definitions, the number and percentage of subjects with a clinical response and no clinical response will be summarized by treatment group in the ITT Analysis Set. Exact 2-sided 95% confidence intervals for the point estimates of the clinical response rates in each treatment group will be determined using the Clopper-Pearson method. The odds ratio (omadacycline /placebo) and p-value will be calculated using Cochran-Mantel-Haenszel test, stratified by prior antibiotic use.

Secondary efficacy endpoints based on patient-reported outcomes and quality of life assessments and microbiologic assessments will also be analyzed to provide supportive evidence of efficacy.

Data Monitoring Committee:

No data monitoring committee planned for this study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

BSSSI	acute bacterial skin and skin structure infections
AE	adverse event
ANCOVA	analysis of covariance
ATCC	American Type Culture Collection
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC	area under the concentration-time curve
β-hCG	serum β-human chorionic gonadotropin
CABP	community-acquired bacterial pneumonia
CGI-I	Clinical Global Impression – Global Improvement Scale
CGI-S	Clinical Global Impression – Severity of Illness
CI	confidence interval
CSA	clinical study agreement
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
iv	intravenous
IxRS	interactive voice/web response system
LS	least squares
MABc	*Mycobacterium abscessus complex*

MAC	*Mycobacterium avium* complex
MIC	minimum inhibitory concentration
NTM	nontuberculous mycobacterial
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	principal investigator
PK	pharmacokinetics
PRO	patient-reported outcomes
PROMIS Short Form v1.0 – Fatigue 7a Daily	Patient-Reported Outcomes Measurement Information System Short Form v1.0 – Fatigue 7a Daily
PT	preferred term
q24h	every 24 hours
QOL-B	Quality of Life – Bronchiectasis
REB	Research Ethics Board
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SE	standard error
SGRQ	St. Georges Respiratory Questionnaire
SOC	system organ class
US	United States

1 DISCLOSURE STATEMENT

Restricted Distribution of Documents

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2 CONTACTS

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3 INTRODUCTION

3.1 Nontuberculous Mycobacterial Pulmonary Disease

More than 140 nontuberculous mycobacterial (NTM) species have been identified, with more than half of the NTM pulmonary infections in the United States (US) associated with *Mycobacterium avium* complex (MAC) (Prevots 2010; Spaulding 2017). *Mycobacterium abscessus* complex (MABc) is the second most common NTM grouping causing human disease in the US, comprising about 10% of all NTM pulmonary infections across various study sites (Prevots 2015). In 2010, the number of national cases of NTM pulmonary infections was estimated as 86,244 (Strollo 2015). More recently in 2019, the number of NTM pulmonary cases was estimated to be as high as 115,000 nationally (Insmed Presentation 2021). The annual prevalence of NTM pulmonary infections in the US in 2015 was estimated as 11.7 per 100,000, representing a 7.5% annual increase from 2008 (Winthrop 2020).

Infections caused by MABc are notoriously difficult to treat due to intrinsic resistance to many classes of antibiotics. Few oral antibiotics demonstrate in vitro activity against MABc, making long-term treatment extremely difficult. Currently there are no Food and Drug Administration (FDA)-approved treatments for pulmonary disease caused by MABc. Current treatment options (off-label treatments) are typically lengthy and require complex, multidrug regimens (Strnad 2018). *M. abscessus* isolates display in vitro resistance to most oral antibiotics and are generally susceptible to a limited number of parenteral agents. Previous guidelines recommend using a multidrug regimen including ≥ 2 of these antibiotics to which the organism is susceptible in vitro. Recent work suggests a lack of consensus among treating physicians, with a variety of regimens employed against this organism ranging from 2 to 5 drugs in the initial phases of therapy (Daley 2020).

Most of the antibiotics recommended for the treatment of MABc pulmonary infection have safety and tolerability profiles that are not conducive to an extended treatment course. Current treatment regimens are frequently associated with serious adverse effects and poor patient adherence contributing to poor clinical outcomes. With these current treatment challenges, expert NTM clinicians and patient advocacy groups have emphasized the urgent need for developing new antibiotics for the treatment of NTM infections. Ideally, these antibiotics would have potent in vitro activity and a high barrier to the emergence of resistance. A favorable safety and tolerability profile and the availability of an oral formulation both take on added importance because of the anticipated prolonged treatment duration. An antibiotic with these properties has the potential to improve both microbiologic and patient quality of life outcomes in patients with MABc pulmonary disease.

Therefore, a clear unmet need exists for an effective and safe antibiotic that is well-tolerated and can be administered orally. Omadacycline has the potential to fill this unmet need.

3.2 Omadacycline

The investigational product, omadacycline (formerly named PTK 0796), is the first member of the aminomethylcycline class of antibiotics, which are semisynthetic derivatives of the

tetracycline class. As a class, tetracyclines have been in use for approximately 70 years. They are well-tolerated and have proven effective in the treatment of a variety of bacterial infections. Intravenous NUZYRA (omadacycline) and oral NUZYRA tablets have been approved by the US FDA for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible microorganisms.

While data from the completed nonclinical program supports dosing up to 90 days, this is the first clinical trial that will administer study dosing of omadacycline beyond 14 days of therapy. Current-use data indicate that omadacycline is being used for chronic dosing without any safety signal identified, through Paratek's post-marketing pharmacovigilance program and published cases studies. Review of post-marketing off-label use reports did not reveal any trends or recommended updates to the current reference safety information. As of January 2021, 5 case series have been published that together report experience on 19 patients with NTM infections, predominately *M. abscesses* (Frizzell 2020; Gill 2019; Minhas 2019; Morrisette 2021; Pearson 2020). Patients were treated with oral omadacycline for periods ranging from 4 weeks to 20.6 months, all but one as part of a multidrug regimen. Omadacycline was overall safe and well-tolerated. Clinical success was reported in 16 patients. Reported events were consistent with the established safety profile and are not unexpected. These real-world observational reports of treatment with omadacycline for NTM provide support to progress to a randomized controlled trial setting, including long-term dosing.

Please refer to the current version of the Investigator's Brochure for additional information on omadacycline.

3.3 Properties of Omadacycline that Address the Unmet Treatment Need for *M. abscessus* Complex Pulmonary Infection

Omadacycline has several key characteristics that may prove beneficial to patients with MABc pulmonary infection:

- Potent in vitro activity versus *M. abscessus* complex subspecies
  - No antagonism in vitro when tested in combination with other antimicrobials commonly used to treat *M. abscessus* infections
- Demonstrated efficacy in a mouse model of *M. abscessus* pulmonary infection
- Favorable pharmacokinetics (PK) and dosing regimen
  - Extensive penetration into lung tissue compartments including epithelial lining fluid and alveolar macrophages
  - Half-life of 17 hours supports once-daily dosing
  - No dosing adjustments are required for age, weight, race, sex, renal or hepatic impairment
- Established safety profile in pre-clinical studies and Phase 3 clinical trials conducted in CABP and ABSSSI populations (up to 14 days of dosing)
  - Does not prolong the QTc interval

- No cases of C. difficile infections reported in clinical trials
- Not metabolized by cytochrome P450 enzymes, no metabolic drug-drug interactions

- Expected safety of a tetracycline class antibiotic when administered for extended durations of treatment. Tetracyclines have a well-established safety profile in the treatment of various chronic disease states.
- Demonstrated efficacy and safety in elderly patients and patients with common co-morbidities in clinical trials conducted in CABP and ABSSSI populations
  - Elderly (≥ 65 years including a subset of patients ≥ 75 years of age)
  - Chronic obstructive pulmonary disease
  - Diabetes mellitus
  - Mild to moderate renal impairment

4 STUDY OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
Efficacy: To evaluate the efficacy of omadacycline in adult subjects with NTM pulmonary disease caused by MABc based upon subject assessment of symptoms	Including but not limited to: • Clinical response at Day 84 defined as improvement in severity of at least 50% of the symptoms present at baseline • Clinical response at Day 84 defined as improvement in severity of at least 50% of the symptoms present at baseline and no deterioration in severity of symptoms present at baseline
Safety: To evaluate the safety and tolerability of omadacycline in adult subjects with NTM pulmonary disease caused by MABc	• Incidence of adverse events (AEs) and serious adverse events (SAEs) • Change from baseline for: o Clinical laboratory parameters o Vital signs o Electrocardiograms (ECGs) • Incidence of potentially clinically significant: o Clinical laboratory parameters o Vital signs o ECGs

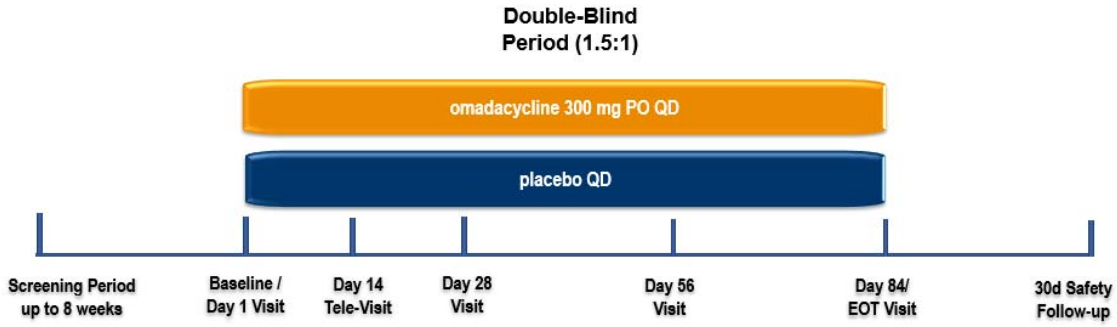
Secondary	
To evaluate patient-reported outcomes (PROs) and quality of life in adult subjects with NTM pulmonary disease caused by MABc	• Quality of Life – Bronchiectasis (QOL-B) • St. Georges Respiratory Questionnaire (SGRQ) • Patient-Reported Outcomes Measurement Information System Short Form v1.0 – Fatigue 7a Daily (PROMIS Short Form v1.0 – Fatigue 7a Daily) • Patient Global Impression of Change (PGI-C) • Patient Global Impression of Severity (PGI-S) • Clinical Global Impression – Severity of Illness (CGI-S) • Clinical Global Impression – Global Improvement Scale (CGI-I) • No new symptom (ie, symptom not present at baseline) with severity worse than mild
To evaluate the microbiological response of omadacycline in adult subjects with NTM pulmonary disease caused by MABc	• Decrease in quantitative sputum culture at Day 84 • Time to growth in liquid medium only • Time to first negative sputum culture

5 INVESTIGATIONAL PLAN

5.1 Overall Study Description

This is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multi-center study in adults with NTM pulmonary disease caused by MABc. The study design is shown in Figure 1.

Figure 1. Study Design Schema



Following a Screening period of up to 56 days (8 weeks) prior to dosing, eligible subjects will be randomized (1.5:1) to receive either 300 mg once daily oral omadacycline monotherapy or matching placebo. Subjects will be stratified according to their use of prior antibiotics for treatment of MABc NTM infection (received prior treatment vs. no prior treatment).

Subjects will attend monthly visits during the approximately 84 day (3-month) double-blind treatment period. In addition, subjects will complete a 14-day safety tele-visit as well as a safety follow-up call approximately 30 days after their last dose of test article. Total duration of subject participation is approximately 5 months.

Refer to the Schedule of Assessments for a complete summary of subject visits and assessments.

5.2 Rationale for Study Design

This study is intended to assess the safety and efficacy of omadacycline in addition to non-pharmacologic standard of care in NTM subjects caused by MABc. Non-pharmacologic measures, including patient education, airway clearance technique, inspiratory muscle training, and exercise training, are considered the first line of therapy in these subjects and will be permitted during the study (Lan 2020). A 3-month, monotherapy, placebo-controlled study design will allow the best assessment of omadacycline without any confounding

influence of other antibiotic treatments and will provide valuable, controlled data as well as adequate time to observe a treatment effect.

5.3 Approximate Duration of Study

The study is expected to be clinically complete in approximately 28 months.

5.4 Approximate Number of Subjects

Approximately 75 subjects (45 omadacycline and 30 placebo) will be enrolled at approximately 20 sites within the US.

6 STUDY POPULATION SELECTION

Each subject must participate in the informed consent process and sign and date an IRB/IEC/REB-approved informed consent form (ICF) before any procedures specified in this protocol are performed.

6.1 Study Population

This study will evaluate adult subjects with NTM pulmonary disease caused by MABc.

6.2 Inclusion Criteria

Subjects must meet all of the following criteria at Screening and/or Baseline to be eligible to participate in the study:

1. Written and signed informed consent must be obtained before any protocol-specific assessment is performed.
2. Male and female subjects age 18 years or older.
3. Diagnosed MABc pulmonary disease as per Infectious Diseases Society of America/American Thoracic Society guidelines criteria. Subjects must have:
   - At least 2 of the following NTM-infection symptoms at Screening and Baseline:
     - Chronic cough, coughing up blood (hemoptysis), wheezing, chest pain, frequent throat clearing, phlegm or sputum production, shortness of breath, fatigue, fever, night sweats, poor appetite, and/or weight loss
   - At least 1 positive pulmonary culture for MABc in the 6 months prior to Screening and 1 positive culture at Screening (note: prior culture and screening cultures must be at least 30 days apart).
   - Radiographic evidence of MABc infection via computed tomography (CT) scan of the chest within 3 months prior to Screening with findings consistent with NTM pulmonary disease. If no CT scan obtained within previous 3 months, one should be performed at Screening to confirm eligibility.
4. Based on the clinical assessment of the investigator, guideline-directed antibiotic therapy for treatment of MABc will not be required within the next 3 months, and a delay, in order for the subject to participate in a placebo-controlled clinical trial, is considered reasonable and clinically acceptable.
5. Be able to produce approximately 5 mL of sputum via spontaneous expectoration or be willing to undergo sputum induction to produce approximately 5 mL of sputum for microbiological evaluation.
6. Females must have a negative serum pregnancy test and agree to use a highly effective form of birth control (eg, abstinence, oral contraceptive, intrauterine device, or barrier contraception [eg, condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through study completion. Males (if sexually active) must agree to use a highly effective method of birth control with female partner(s) from Screening through study completion.

7. Able and willing to adhere with the requirements and restrictions of the study.

6.3 Exclusion Criteria

Subjects meeting any of the following criteria at Screening and/or Baseline will be excluded from participation in the study:

1. Pregnant or nursing (breastfeeding) women.
2. Has received antibiotic treatment within 6 months prior to Screening for MABc or MAC.
3. Has received systemic or inhaled antibiotic therapy (other than chronic macrolide therapy) within 4 weeks prior to Screening.
4. Is experiencing an exacerbation of an infection with a non-*Mycobacterium* species (eg, *Pseudomonas aeruginosa*) that the investigator considers clinically relevant.
5. Has any of the following medical conditions:
   - Active pulmonary malignancy (primary or metastatic), or any type of malignancy requiring chemotherapy or radiation within 1 year prior to Screening.
   - Active allergic bronchopulmonary mycosis, or any other condition requiring chronic treatment with systemic corticosteroids (ie, prednisone dose ≥ 15 mg/day for a period of ≥ 4 consecutive weeks above this level; see Appendix 2) within 90 days prior to Screening.
   - Radiologic evidence of cavitary disease.
   - Known active pulmonary tuberculosis.
   - Cystic fibrosis.
   - History of lung transplantation.
   - Another advanced lung disease with a known percent predicted forced expiratory volume in 1 second < 30%.
   - Disseminated or extra-pulmonary NTM disease.
6. Screening calculated creatinine clearance < 30 mL/minute, using the Cockcroft-Gault equation (Appendix 2), requirement for any form of dialysis (eg, hemodialysis, peritoneal dialysis), or other evidence of severe renal disease.
7. Has any of the following at Screening:
   - Alanine aminotransferase or aspartate aminotransferase ≥ 3 × upper limit of normal.
   - Total bilirubin > 1.5 × upper limit of normal.
   - Suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy).
8. History of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening.
9. Significant immunological disease determined by any of the following:
   - Current or anticipated neutropenia defined as < 500 neutrophils/mm^3.
   - Known infection with human immunodeficiency virus (HIV).

10. History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline, tigecycline, or omadacycline).
11. Has been previously treated with omadacycline.
12. History of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
13. Systemic treatment with disease-modifying antirheumatic agents, corticosteroids (equivalent to prednisone dose ≥ 15 mg/day for a period of ≥ 4 consecutive weeks above this level) or immunosuppressive agents in the 90 days prior to Screening.
14. Has current evidence of active pancreatitis.
15. Evidence or history of any other clinically significant medical condition or planned medical intervention that may, in the opinion of the investigator, pose a significant safety risk, impair study participation, impact the subject's ability to undergo the required study procedures or ability to complete the expected course of study treatment.
16. Any surgical or medical condition that, in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism, or excretion of drugs.
17. Inability to fast for 4 hours prior to dosing and/or 2 hours after dosing.
18. Per discretion of the investigator, subject is not expected to survive the duration of the study.

6.4 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before random assignment to double-blind treatment are defined as screen failures. All screen failures should be recorded on the subject master list. Limited information including reason for screen failure will be recorded on the electronic case report form (eCRF) or interactive voice/web response system (IxRS) system for screen failures. Screen failure subjects may be re-screened at the discretion of the investigator and in consultation with the medical monitor as needed. Any subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened.

7 STUDY TREATMENT(S)

7.1 Treatments Administered

Test articles will be supplied by Paratek Pharmaceuticals, Inc. (the sponsor). Test articles will be labeled according to regulations.

The test articles should be administered only to subjects who have provided informed consent and who meet all of the inclusion criteria and none of the exclusion criteria. Once the test article has been assigned to a subject, it must not be reassigned to another subject.

Following a Screening period of up to 56 days (8 weeks), eligible subjects will be randomly assigned to receive 300 mg oral omadacycline or matching placebo tablets.

7.2 Identity of the Investigational Product: Omadacycline

Oral Formulation (Omadacycline)

Name	**Omadacycline Tablet, 150 mg**
[redacted]	

Placebo

Name	**Placebo tablets**
Excipients	Lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate
How supplied	Tablets are packaged in an alu/alu 6-count (2 × 3) foil blister. Secondary packaging will consist of fold-over, child-resistant blister cards (2 blisters per card) and patient kits containing 6 blister cards (72 tablets per patient kit)
Storage	Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature)
Preparation and handling	No special requirements
Administration	Please see Section 7.5

7.3 Dose Selection Rationale

The dosing regimen of omadacycline selected for this study is based on the demonstration of efficacy in a mouse model of *M. abscessus* pulmonary infection, as well as the totality of nonclinical and clinical experience to date, including in vitro antibacterial activity, PK characteristics, and the overall safety and tolerability profile of the FDA-approved dosing regimens for treatment of CABP and ABSSSI.

In a nonclinical C3HeB/FeJ mouse model of *M. abscessus* pulmonary infection, omadacycline efficacy was demonstrated using the dose best representing the human equivalent exposure ie, area under the concentration-time curve (AUC) of the human 300 mg oral dose. The C3HeB/FeJ mouse was previously demonstrated to provide utility as a mouse model of *M. abscessus* pulmonary infection for antibacterial studies (Maggioncalda 2020; Story-Roller 2019). Administration of a corticosteroid (dexamethasone) allows for initial proliferation of and subsequent sustained *M. abscessus* pulmonary infection and pathology following infection via an aerosolized route.

As detailed in the Investigator's Brochure, the steady state AUC (hr*µg/mL) for the 300 mg oral dose is 11.156, while the steady state free AUC (hr*µg/mL) of the 300 mg oral dose is 8.92 (adjustment for free fraction by 20% human plasma protein binding; on file at Paratek). Therefore, a mouse dose was selected to represent a steady state free AUC (hr*µg/mL) of approximately 9.

Omadacycline PK parameters in C3HeB/FeJ mice were determined after subcutaneous administration of omadacycline doses of 7.5, 15 and 30 mg/kg in order to calculate the appropriate mouse dose to study in the efficacy model. Following determination of key PK parameters, adjustment for free fraction in mice (33.9% mouse plasma protein binding; data on file at Paratek), and graphical assessment of the mouse free area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) (hr*µg/mL) versus mouse doses studied, the resulting linear equation was utilized to calculate the appropriate mouse dose. Specifically, the data demonstrated that a mouse subcutaneous dose of approximately 15 mg/kg every 24 hours (q24h) best represents a human AUC_{0-24} (hr* µg/mL) of 9 (on file at Paratek).

The American Type Culture Collection (ATCC) reference strain *M. abscessus* 19977 (omadacycline minimum inhibitory concentration [MIC] values of 0.25 to 0.5 µg/mL) and the clinical isolate M9501 (omadacycline MIC value of 0.25 µg/mL) were evaluated in the mouse model of efficacy (MIC data on file at Paratek). Mice were infected via aerosolization and treatment was initiated 1-week post-infection. Mice were treated with either omadacycline (15 mg/kg q24h), imipenem (200 mg/kg every 12 hours; positive control) or vehicle (phosphate buffered saline; q24h) for 4 weeks and the bacterial burden in the lungs was evaluated at various timepoints (0, 1 week, 2 weeks, and 4 weeks) throughout the study. Efficacy was determined as a reduction in lung bacterial burden compared to vehicle controls.

M. abscessus lung burden in the vehicle control group increased throughout the course of infection as expected. In the positive control group (imipenem treatment), *M. abscessus* lung burden decreased gradually over the duration of the study. For mice infected with the

reference strain ATCC 19977, at the final timepoint of 4 weeks of treatment, omadacycline produced >3 $\log_{10}$ reduction in total lung colony forming units compared to mice in the vehicle control group. Similarly, omadacycline treatment reduced lung burden of the clinical strain M9501 by 2 $\log_{10}$ at the conclusion of 4 weeks of treatment.

Therefore, based on the demonstration of omadacycline efficacy in the mouse model of *M. abscessus* pulmonary infection at the equivalent human steady state free AUC (hr*µg/mL) of approximately 9, the 300 mg oral dose will be evaluated in this human clinical study.

Phase 3 clinical trials in CABP and ABSSSI have demonstrated that omadacycline has an acceptable safety profile. Additionally, the 300 mg oral dose being used in this study has been approved by the FDA for these indications.

7.4 Description of Treatments

Subjects will be randomized (1.5:1) to 1 of the following treatment groups:

- Group 1: 300 mg oral omadacycline (2 × 150 mg tablets administered once daily, q24h)
- Group 2: Placebo tablets resembling omadacycline (2 tablets administered once daily, q24h)

7.5 Test Article Administration

7.5.1 Oral Administration of Test Article

All doses of oral test article should be taken with water once daily, at approximately the same time of day.

All doses should be taken in a fasted state. Fasting is defined as no food, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) or drink except water for at least 4 hours before dosing. After dosing, no food or drink (except water) is permitted for 2 hours and no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

7.6 Dose Adjustments and Interruptions of Test Article

No dose adjustments or planned interruptions of test article will be permitted during this study.

7.7 Method of Assigning Patients to Treatment Groups

All eligible subjects will be randomized via an IxRS that assigns them to the treatment group in a 1.5 to 1 ratio (omadacycline: placebo). The site delegate will contact the IxRS after confirming that the subject fulfills all the inclusion criteria and has none of the exclusion criteria. The IxRS will assign a test article to the subject based on a computer-generated

randomization schedule. The randomization will be a blocked randomization sequence stratified by prior antibiotic use for treatment of MABc NTM infection (prior antibiotic use and no prior antibiotic use) as defined in the IxRS specifications. Subjects randomized into the study will be assigned the treatment corresponding to the next available number from the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, regardless of whether the subject actually receives any test article.

7.7.1 Subject Numbering

Upon the subject signing the informed consent, site personnel should enter the subject in the IxRS, and the subject will be assigned a unique subject number. Subjects who have been pre-screened but who do not sign an ICF will not be assigned a subject number. A subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened. Re-screening is at the discretion of the investigator and in consultation with the medical monitor. The investigator will maintain a subject master list to document every subject who has signed an ICF using the subject number assigned by the IxRS. A copy of this list should be retained in the investigator's study files.

7.8 Dispensing Test Article

Each study site will be supplied by the sponsor with the test article. Oral test article supplies are completely blinded, and blinded study personnel can conduct storage, dispensation, and reconciliation. The IxRS will assign the test article kit to be given to the subject.

Oral test article will be supplied to the sites in labelled, blinded kits that contain 6 blister cards (12 tablets per card, 72 tablets per kit) of omadacycline (150 mg) tablets or matching placebo tablets. Each kit contains enough test article for 4 weeks of test article administration between visits. At each visit when test article is dispensed (Baseline, Day 28, Day 56), study personnel will access the IxRS and be assigned a test article kit to be given to the subject. The study coordinator/staff will instruct the subject on the use of oral test article.

7.9 Blinding

The investigator and sponsor will be blinded to treatment group assignments throughout the study. The sponsor designee (eg, clinical supply manager, IxRS vendor, etc.) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained and that only sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes).

Randomization data are kept strictly confidential until the time of database lock and unblinding at the end of the study. Unblinded treatment assignments will be provided to study sites after the study has concluded.

All test articles will be supplied in identical packaging thereby maintaining the blinding for all site staff and subjects.

Unblinding by site personnel is only to occur in the case of subject emergencies (see Section 7.10, below).

7.10 Emergency Unblinding of Treatment Assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, test article discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. It is encouraged for the investigator, when contemplating unblinding, to contact the sponsor or sponsor's designated medical monitor or designee to confirm the need to unblind, prior to unblinding (see Section 2 for contact information). However, if required, the investigator can unblind without consulting the medical monitor.

Emergency code breaks are performed using the IxRS. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the drug treatment for the specified subject and a fax or e-mail confirming that the treatment assignment of the subject was unblinded. The system will automatically inform the sponsor's monitor and the sponsor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place at their site to allow access to the IxRS code break information in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

All steps outlined above will be followed, including contacting the medical monitor as soon as possible and not more than 24 hours afterwards. It will be the responsibility of all study personnel to ensure that, except for the above procedure, investigator blinding is maintained until after study completion.

7.11 Prior and Concomitant Therapy

- All antibiotics administered for the subject's MABc or MAC infection within 2 years prior to the date of informed consent will be recorded in the eCRF.
- All significant non-pharmacological therapies related to MABc infection including patient education, airway clearance technique, inspiratory muscle training, and exercise training administered from 30 days prior to date of informed consent, and administered throughout the duration of the study through the 30-day follow-up period, will be recorded in the eCRF.
- All pharmacological therapies (regardless of indication) that have been administered from 7 days prior to the date of informed consent and administered throughout the duration of the study through the 30-day follow-up period, will be recorded in the eCRF.

- All significant non-pharmacological therapies not related to MABc infection administered from 7 days prior to date of informed consent, and administered throughout the duration of the study through the 30-day follow-up period, will be recorded in the eCRF.

7.12 Prohibited Therapy

The following therapies (including timeframe for exclusion) are prohibited:

- Antibiotic treatment for MABc or MAC infection (including systemic or inhaled antibiotics) within 6 months prior to Screening and through Day 84/end of treatment (EOT) visit
- Systemic or inhaled antibiotic therapy (other than chronic macrolide therapy) within 4 weeks prior to Screening and through Day 84/EOT visit
- Systemic treatment with disease-modifying antirheumatic agents, corticosteroids (equivalent to prednisone dose ≥ 15 mg/day for a period of ≥ consecutive 4 weeks above this level) or immunosuppressive agents within 90 days prior to Screening and through Day 84/EOT visit
- Use of isotretinoin within 2 weeks prior to Screening and through Day 84/EOT visit
- Subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours before and within 4 hours after oral doses

7.13 Permitted Treatments

All other treatments not specified as prohibited are permitted during the study. Subjects requiring additional or alternative therapy for their MABc NTM pulmonary disease will be discontinued from test article. Further treatment for their infection is at the discretion of the investigator or the subject's health care provider and will be considered as a concomitant medication.

Subjects should be encouraged to contact site personnel before starting any new treatment.

7.14 Treatment Compliance

Subjects will record daily test article dosing information in a paper diary. Study personnel at the site should monitor oral test article compliance at each study visit by comparing the returned test article with the dosing information reported by the subject. Compliance and any unresolved discrepancies will be documented in the source document and on the drug inventory record. The test article eCRF should reflect the reconciled dosing information provided by the subject.

7.15 Packaging and Labeling

The investigational test article, omadacycline, and the placebo will be packaged by the sponsor and supplied to the investigator.

7.16 Storage and Accountability

Test article must be received at the study site by a designated person, acknowledged in the IxRS, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, the test article should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored, and appropriate temperature logs maintained as source data.

The designated study personnel must maintain an accurate record of the shipment and dispensing of test articles. Test article supplies are completely blinded. Subjects will be asked to return all unused test article and packaging at each visit and at the end of the study, last study visit or at the time of test article discontinuation. Monitoring of oral test article accountability will be performed by the field monitor during site visits and at the completion of the study.

7.17 Investigational Product Retention at Study Site

At the conclusion of the study, and as appropriate during the course of the study, with instruction and approval from the sponsor, the designated study personnel will destroy on site as permitted by local site operating procedures, or return all unused test articles, packaging, and drug labels. Test articles can only be returned or destroyed after the sponsor has performed accountability. Destruction/return of all test article will be documented and maintained in the site files.

8 STUDY PROCEDURES

Written, signed, and dated informed consent will be obtained before any study-related procedures have been performed. Upon signing the informed consent, the subject will be assigned a study subject number. Subjects who have been pre-screened but who do not sign an ICF will not be assigned a subject number. The investigator will maintain a subject master list to document every subject who has signed an ICF using the subject number assigned by the IxRS. A copy of this list should be retained in the investigator's study files.

A study Schedule of Assessments is provided in Appendix 1.

8.1 Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC/REB-approved ICF

Subjects will also have the option to provide consent for collection of serum and plasma for biomarkers. This is not required for subject eligibility and participation (See Section 8.11).

8.2 Subject Demographics/Other Baseline Characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include date of birth (per local regulations), gender, and race/ethnicity.

8.3 Medical History

The investigator will perform a comprehensive history at the Screening visit. Significant medical history (at any time) and any medical history within the past 6 months including ongoing medical conditions at the time of signing of the ICF will be recorded.

Where possible, diagnoses are to be recorded. Any event or change in the subject's condition or health status occurring after signing the ICF will be reported as an AE.

8.4 Physical Examination

At Screening and Day 84/EOT, a full physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems.

Information for all physical examinations must be included in the source documentation at the study site. Relevant findings that are present prior to the start of test article must be included in the relevant medical history/current medical conditions screen on the subject's eCRF. New clinically significant findings made after the start of test article which meet the definition of an AE must be recorded as an AE in the subject's eCRF.

8.5 Vital Signs

Vital signs including blood pressure, heart rate, body temperature, and pulse oximetry will be measured at the timepoints as specified in Appendix 1.

The subject's vital signs should be captured after at least 5 minutes (+ 5 minutes) of rest while in a non-standing position (supine or sitting). Subsequent vital sign measurements should be captured in the same non-standing position.

8.6 Height, Weight and Body Mass Index

Height and body weight should be obtained with the subject's shoes off and recorded in the eCRF at the timepoints as specified in Appendix 1. Body mass index will be automatically calculated upon entry of height and weight in the eCRF.

8.7 Electrocardiogram

A standard 12-lead ECG should be obtained using site equipment. The ECG will be obtained after the subject has been in a semi-recumbent position for approximately 10 minutes at the Screening and Day 84/EOT Visit. Reading and interpretation of the ECG will be performed locally by the investigator, and hard copies of the reports retained in the files.

8.8 Computed Tomography Scan – Chest

Computed tomography scans of the chest will be performed using site equipment or local radiology facility. High resolution CT scan is preferred, if available. The CT scan will be interpreted by appropriately qualified personnel who are certified or licensed to interpret chest radiographs according to applicable regional requirements, reviewed by the investigator or qualified personnel and the conclusions of this review will be the basis for subject inclusion. The review report should be included in the source documents.

Sites may utilize results of a chest CT scan performed within 3 months prior to Screening to determine eligibility (radiographic evidence of MABc infection). If no CT scan was obtained within the 3 months prior to Screening, a CT scan will be required at Screening. A follow-up chest CT scan will also be performed at the Day 84/EOT visit.

8.9 Clinical Laboratory Tests

8.9.1 Central Safety Laboratory Parameters

A Central Laboratory will be used for safety analysis of all specimens collected. Details on the collection tubes and containers, shipment of samples and reporting of results by the Central Laboratory are provided to investigators in the Central Laboratory Manual.

The total volume of blood collected from each subject will be approximately 10.5 mL (2 teaspoons) per visit, or approximately 42 mL (3 tablespoons) over the course of the study.

Clinical laboratory tests for safety will include the following:

Table 1. Clinical Laboratory Tests (Central)

Hematology: • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential Coagulation: • Prothrombin time international normalized ration (INR) Pregnancy (all female subjects): • Serum β-human chorionic gonadotropin (β-HCG)	Serum Chemistry: • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Creatine phosphokinase (CK) • Gamma-glutamyl transpeptidase (GGT) • Glucose • Lipase • Magnesium • Phosphorus (P) • Potassium (K) • Sodium (Na) • Total bilirubin

8.9.2 Local Safety Laboratory Parameters

All female subjects will have a local urine or serum pregnancy test at the site during Screening and at the Baseline Visit (just prior to randomization). Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine or serum pregnancy test result is obtained at the site during Screening or at the Baseline Visit, the subject is not to be randomized.

A serum sample for serum β-human chorionic gonadotropin (β-hCG) testing will be collected and sent to the Central Laboratory for confirmation of the local urine or serum pregnancy test results. If a positive β-hCG result is reported by the Central Laboratory after a subject is enrolled, test article administration should be discontinued.

8.10 Sputum Collection For Microbiology

A Central Specialty Microbiology Laboratory will be used for analysis of all sputum specimens. Details on the collection supplies, shipment of samples and reporting of results are provided to investigators in the Central Laboratory Manual.

Pre-dose expectorated or induced sputum specimens (approximately 5 mL) will be collected at all timepoints as indicated in Appendix 1. To improve the probability of obtaining a good sputum specimen, at least 2 and preferably 3 spontaneously expectorated sputum samples will be obtained from subjects at each timepoint. During Screening, samples will be collected after the subject signs the informed consent. For all subsequent visits, sputum samples should be collected on 2 to 3 consecutive days (when possible), just prior to, and up through the day of the scheduled visit.

If a subject is unable to produce sputum spontaneously and independently, sputum induction may be performed by appropriately qualified site staff to obtain one induced sputum specimen. Please refer to Appendix 3. If a subject is still unable to produce sputum despite reasonable efforts at any visit post-Baseline, this will be considered as a negative culture result at that timepoint. Sterile, leak proof, non-wax, disposable plastic containers will be used to collect specimens. Detailed instructions will be provided by site staff to subjects on how to collect and handle samples aseptically to avoid contamination. Subjects will also be instructed to keep sputum samples refrigerated, not frozen, until ready to transport to the site. Upon receipt at the site, samples should be kept refrigerated until ready to ship to the central specialty microbiology lab. Shipping should occur within approximately 2 days of receipt from subject to avoid overgrowth by contaminating normal flora. No fixative or preservatives are to be used with sputum samples. Detailed instructions for collecting, processing, and shipping sputum specimens will be provided in the Central Laboratory Manual.

The Central Specialty Microbiology Lab will process the sputum specimens. Acid fast bacilli smear testing from sputum will be performed on all specimens received. Specimens will be further cultured in both solid and liquid media and identification of genus and species will be performed, to the subspecies level for *M. abscessus*. Results confirming *M. abscessus* infection will be used to verify subject eligibility during Screening.

In vitro susceptibility testing of antimicrobial drugs that may be used to treat *M. abscessus* pulmonary infection will be performed, and molecular characterization for select drug resistance markers will be performed. Susceptibility results will not be reported to site personnel during the study.

8.11 Serum and Plasma Collection for Biomarkers (*optional*)

Serum and plasma for biomarkers will be collected and stored at a central laboratory for future use for all subjects who provide consent for this optional portion of the study.

Samples may be stored for a period of up to 2 years after the completion (termination) of the study, or longer, to see if there may be indicators associated with NTM lung infections and

for other exploratory analyses. Genetic testing or analysis will not be performed on any samples collected.

8.12 NTM Symptom Assessment Questionnaire

The NTM Symptom Assessment Questionnaire is a tool created by Paratek to evaluate efficacy based on individual subject assessment of symptoms. It is a self-administered questionnaire that evaluates a list of 12 common NTM symptoms, asking subjects if they have experienced each symptom within the past 7 days. Responses are provided using a 4-point scale (absent, mild, moderate, severe) and should reflect the subject's perceived overall impression of their symptoms over the past 7 days. This questionnaire is completed by the subject without interpretation of the subject's response by a clinician or site staff.

In addition, at Screening, subjects will be asked to list up to 3 of their most bothersome symptoms.

The NTM Symptom Assessment Questionnaire will be completed at Screening, Baseline/Day 1 (prior to first dose of test article), and the Day 28, Day 56, and Day 84/EOT Visits. Responses at Screening and Baseline/Day 1 will be used to determine eligibility.

8.13 Other Patient-Reported Outcomes and Clinician-Assessed Outcomes

Patient-reported outcomes are being utilized in this study to help understand and assess the subject's health, quality of life or functional status associated with the disease under study and treatment received. The PROs are completed by the subject without interpretation of the subject's response by a clinician or site staff but should be reviewed for completeness and to assess potential AE information.

All PROs described below will be completed the Day 28, Day 56, and Day 84/EOT visits. In addition, the QOL-B, SGRQ, and PROMIS Fatigue will be collected at Day 1/Baseline visit (prior to first dose of test article).

8.13.1 Quality of Life – Bronchiectasis

The QOL-B is a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for patients with non-cystic fibrosis bronchiectasis using a series of 37 questions.

8.13.2 St. Georges Respiratory Questionnaire

The SGRQ is a self-administered questionnaire that assesses health-related quality of life in subjects with chronic pulmonary disease by evaluating 3 health domains:

- symptoms (distress caused by respiratory symptoms)
- activity (effects of disturbances to mobility and physical activity)
- impacts (the effect of disease on factors such as employment, personal control of one's health, and need for medication)

8.13.3 Patient-Reported Outcomes Measurement Information System Short Form v1.0 – Fatigue 7a Daily

The PROMIS Fatigue is a self-administered questionnaire that assesses fatigue and its impact on physical, mental, and social activities. The fatigue short form is universal rather than disease-specific and assesses fatigue over the past 7 days.

8.13.4 Patient Clinical Impression of Severity

The PGI-S is a self-administered, single question assessed using a 7-point scale that measures a subject's perception of disease severity.

8.13.5 Patient Clinical Impression of Change

The PGI-C is a self-administered, single question assessed using a 7-point scale that measures a subject's perceived change in clinical status and overall improvement.

8.13.6 Clinical Global Impression – Severity of Illness

The CGI-S is administered by an experienced clinician who is familiar with the disease under study. The CGI-S is a 1-item observer-rated scale that rates illness severity based upon observed and reported symptoms, behavior, and function over the past seven days.

8.13.7 Clinical Global Impression – Improvement

The CGI-I is administered by an experienced clinician who is familiar with the disease under study and who can make an expert judgment about the total picture of the subject at each visit. The CGI-I is a 1-item observer-rated scale that rates total subject improvement compared to baseline and whether or not, per clinical judgment, it is due entirely to drug treatment.

8.14 Adverse Events

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose of a test article, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
- An AE occurring from abuse (eg, use for nonclinical reasons) of a test article.
- An AE that has been associated with the discontinuation of the use of a test article.

8.15 Serious Adverse Events

An SAE is an AE that:

- Results in death.
- Is life-threatening (see below).
- Requires hospitalization or prolongation of an existing hospitalization (see below).
- Results in a persistent or significant disability or incapacity (see below).
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent any one of the outcomes listed above in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An AE is considered "life-threatening" if, in the view of the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

8.16 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article: If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE.
- Overdose of a test article as specified in this protocol with or without an AE.
- Inadvertent or accidental exposure to a test article with or without an AE.

8.17 Overdose

Any administration of omadacycline of greater than 600 mg within a 24-hour period will be an overdose, regardless of whether the overdose is intentional or accidental. It is a reportable event and the sponsor must be notified within 1 business day.

The physician managing the overdose may order any test he/she thinks is necessary to manage the subject properly.

8.18 Medication Errors

Medication errors are the result of administration or consumption of the wrong product, by the wrong subject, at the wrong time, and/or by the wrong administration route, due to human error.

Medication errors include, but are not limited to, the following:

- The administration and/or consumption of test article that has not been assigned to the subject
- Administration of expired test article

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the SAE Report Form. All other medication errors will be reported by e-mailing the Clinical Test Article Error Incident Report Form to clinicalsafety@propharmagroup.com.

8.19 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the ICF to the time of the Follow-up assessment. The investigator must instruct the subject to report AEs and SAEs during this time period. Reports of death after the last study contact with the subject will be reported to the sponsor and additional information relative to the cause of death will be sought and documented.

All AEs and SAEs must be recorded on source documents. All AEs and SAEs for subjects who receive a treatment assignment will be recorded in the eCRFs.

The investigator must follow up as medically necessary on all AEs and SAEs until the events have subsided, the condition has returned to Baseline, or in case of permanent impairment, until the condition stabilizes.

Adverse events should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded using standard medical terminology.

If an AE requires a surgical or diagnostic procedure, the illness leading to the procedure should be recorded as the AE, not the procedure itself.

Death should be recorded in the eCRF as an outcome of an AE. Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC/REB.

8.19.1 Serious Adverse Event Reporting

All SAEs and follow-up information must be reported within 1 business day or 24 hours as required by local regulations by emailing a completed SAE Report to the email address below.

E-Mail: [redacted]

8.19.2 Assessment of Relatedness

The investigator will assess causality (ie, whether there is a reasonable possibility that test article caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not Related: This relationship suggests that there is no association between test article and the reported event. The event can be explained by other factors such as an underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between test article and the event.
- Related: This relationship suggests that a definite causal relationship exists between test article administration and the AE, or there is a reasonable possibility that the

event was caused by the test article, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Adverse events and SAEs also will be assessed for their potential relationship to the protocol. A protocol-related AE is one that is not related to the test article but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event related to a medical procedure required by the protocol.

8.19.3 Assessment of Severity

The severity (or intensity) of an AE will be classified using the following criteria:

- Mild: These events are usually transient, require minimal or no treatment, and do not interfere with the subject's daily activities.
- Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning but pose no significant or permanent risk of harm.
- Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented as a new event to allow an assessment of the duration of the event at each level of intensity to be performed.

8.19.4 Laboratory Findings

Protocol-defined safety laboratory test results will be analyzed as part of specific laboratory safety analyses. Additional laboratory test results at other timepoints may be available to the investigator as part of standard clinical practice. Throughout the study, laboratory-related abnormalities should be recorded as AEs only if considered clinically significant, outside the range of expected values given the subject's Baseline assessments and clinical course, and not known to be part of another AE diagnosis.

8.19.5 Worsening or Progression of Disease Under Study

Worsening or progression of NTM pulmonary disease caused by *Mycobacterium abscessus* including worsening of baseline symptoms, should not be recorded as an AE unless the worsening/progression also meets the criteria for a serious AE (in which case the event also should be reported as an SAE). If worsening or progression of disease under study requires additional antibiotic therapy, subject will be discontinued from test article and this reason for discontinuation will be recorded in the eCRF.

8.19.6 Pregnancies

To ensure subject safety, each pregnancy in a subject on test article must be reported to the sponsor within 1 business day of learning of its occurrence. Test article should be discontinued immediately, and the pregnancy should be followed up to determine outcome,

including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the test article of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.20 Concomitant Medication Assessments

The investigator should instruct the subject to notify the study site about any new medications they take after the start of the test article.

All prescription medications, over-the-counter drugs, and recreational drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded in the eCRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation dates or indication that the medication continues, and the reason for therapy.

8.21 Subject Discontinuation or Withdrawal

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, worsening of disease under study, lost to follow up, withdrawal by subject, physician decision, death, and other (specify reason eg, subject non-compliance or study termination by the sponsor). Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn from the study if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. In the event a subject is lost to follow-up, every possible effort should be made to contact the subject and determine the reason for discontinuation as local law permits. The due diligence measures taken must be documented in the subject's source documents. If premature withdrawal from the study occurs, the investigator should determine the primary reason for a subject's premature withdrawal from the study and record the date and primary reason on the eCRF. Subjects who discontinue study treatment prematurely should complete the EOT visit and Safety Follow-up assessment, if possible (see Schedule of Assessments – Appendix 1). Exceptions to this include subjects who withdraw consent or are considered lost to follow-up after appropriate due diligence measures have been taken.

Site personnel must also contact the IxRS to register the subject's discontinuation from test article.

For subjects who are lost to follow up, the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the subject (eg, dates of telephone calls, registered letters, etc).

9 STUDY ACTIVITIES

9.1 Screening Period

Screening procedures (as detailed in Appendix 1) may begin once informed consent is obtained and will be used to establish subject eligibility and baseline characteristics for each subject. The Screening period for this study is up to 8 weeks to allow sufficient time for collection and analysis of sputum specimens. Subjects may be randomized as soon as all screening procedures have been performed and results have been received to verify eligibility criteria.

9.2 Double-blind Treatment Period

The double-blind treatment period is approximately 3 months (84 days) in duration. Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be randomized.

In-clinic visits will occur at Baseline/Day 1, Day 28 (± 3 days), Day 56 (± 3 days), and Day 84/EOT (+ 5 days /- 2 days).

A tele-visit (phone call or virtual) will occur at Day 14 (± 2 days) to assess safety via review of AEs and concomitant medications.

9.3 Follow-up Period

9.3.1 30-Day Safety Follow-up Call

The Follow-up assessment should be conducted 30 to 37 days following the subject's last dose of test article to assess safety via review of AEs and concomitant medications. This evaluation should also be conducted for any prematurely withdrawn subject except for subjects who withdraw consent or are lost to follow up. The Follow-up assessment may be conducted via telephone or at the investigator's discretion, the safety follow-up can be an office visit.

10 STUDY SUSPENSION, TERMINATION, AND COMPLETION

10.1 Study Completion and Post-study Test Article

A subject will have successfully completed the study after the planned test article regimen has been administered, and all assessments and visits have been performed up through the final Follow-up assessment. The study will be completed when the last subject has either discontinued or completed the Follow-up assessment.

No long-term follow up of subjects is planned, with the exception of pregnancies, as described in Section 8.19.6, and SAEs described in Section 8.15.

Sites will be notified by either the sponsor or IxRS to stop enrollment when the desired number of treated subjects have been enrolled. Subjects already consented, but not yet randomized, will be allowed to continue screening procedures.

Upon study completion, the investigator will provide the sponsor, IRB/IEC/REB, and regulatory agency with final reports and summaries as required by regulations. The investigator must submit a written report to the sponsor and the IRB/IEC/REB within 3 months after the completion or termination of the study.

10.2 Study Suspension or Termination

The sponsor may suspend or terminate the study or part of the study at any time for any reason. Should termination be necessary, subjects should be seen as soon as possible and treated as described in Section 8.21 for prematurely withdrawn subjects. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or Ethics Committees of the early termination of the study.

If the investigator suspends or prematurely terminates their participation in the study, the investigator will promptly inform the sponsor and the IRB/IEC/REB and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in Section 8.21 for prematurely withdrawn subjects. The investigator will also return all test articles, containers, and other study materials to the sponsor.

11 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator's Brochure, the case report forms and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor monitors the conduct of the study by visiting the site and/or by contacting the site by telephone and e-mail. During these site visits/meetings, information recorded in the case report forms is verified against source documents.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

All analyses of data for this study will comply with International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E9) and the sponsor's guidance documents and standards. Statistical analyses will be performed using Statistical Analysis Software (SAS®).

The statistical analysis plan (SAP) incorporating the sections below, along with mock tables, figures, and listings shells, will be prepared, approved, and finalized by the sponsor prior to database lock. This plan will define populations for analysis, outline all data handling conventions, and specify statistical methods to be used for analysis of safety and efficacy.

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviation, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

All eCRFs must be completed, entered, and source-data verified; all safety and microbiology laboratory results must have been reported; all AEs must have been fully characterized (eg, relationship to test article determined) and coded; and all queries must have been resolved prior to database lock and unblinding. Determination of inclusion in the analysis populations, characterization of protocol deviations as major/minor, and final approval of the SAP will also be completed prior to database lock.

12.2 Determination of Sample Size

As the study is exploratory with respect to determination of efficacy, the sample size determination is provided to better ensure sufficient subjects are enrolled to provide an initial assessment of efficacy rather than test a specific hypothesis. A sample size of 75 subjects will provide approximately 80% power to detect an absolute treatment difference of 30% in clinical response rate at Day 84, based on clinical response rates of 15% and 45% in the placebo and omadacycline treatment groups respectively, using a Mantel-Haenszel test with 2-sided alpha level of 0.05.

12.3 Analysis Populations

The following subject analysis sets have been defined:

- Intent-to-treat (ITT) Analysis Set includes all randomized subjects.
- Per-Protocol Analysis Set includes all randomized subjects who received at least 1 dose of test article and completed the study without major protocol deviations that affect the assessment of efficacy.
- Safety Analysis Set includes all subjects who received at least 1 dose of test article.

12.4 Demographics, Baseline Characteristics, and Subject Disposition

Demographics (including age, gender, ethnicity, and race) and baseline characteristics will be summarized in the ITT Analysis Set by treatment group.

Descriptive statistics of the duration of test article treatment will be provided by treatment group in the ITT and Safety Analysis Sets. The number and percentage of subjects who prematurely discontinued test article and the reason for discontinuation as well as the number and percentage of subjects prematurely discontinuing the study and the primary reason for discontinuation will be presented by treatment group in the ITT Analysis Set.

12.5 Efficacy Endpoint(s)

The study is exploratory with respect to efficacy determination. Efficacy will be evaluated based on endpoints defined by subject-reported NTM symptoms, subject-reported outcomes and quality of life measures, and microbiologic assessment. Additional endpoints to assess efficacy will be defined in the SAP. Nominal p-values will be provided as descriptive statistics.

12.5.1 Primary Efficacy Endpoints

The primary determination of efficacy is based on subject assessment of symptoms. Several definitions of clinical response will be defined, including but not limited to those listed in Section 4; all definitions will be provided in the SAP.

For each definition, the number and percentage of subjects with a clinical response and no clinical response will be summarized by treatment group in the ITT Analysis Set. Exact 2-sided 95% confidence intervals (CIs) for the point estimates of the clinical response rates in each treatment group will be determined using the Clopper-Pearson method. The odds ratio (omadacycline relative to placebo) and p-value will be calculated using Cochran-Mantel-Haenszel test, stratified by prior antibiotic use. The estimand attributes for clinical response will be provided in detail in the SAP. In general, clinical response will use both a treatment and composite policy strategy for handling intercurrent events. Subjects who receive alternative antibiotic therapy for treatment of the NTM infection and/or die before reaching Day 84 will be considered as not achieving clinical response. Subjects with missing data due to withdrawal of consent will also be considered as not achieving clinical response.

Analyses will be repeated in the Per-Protocol Analysis Set as detailed in the SAP.

12.5.2 Secondary Efficacy Endpoints

12.5.2.1 Patient-Reported Outcomes and Quality of Life

For each patient-reported outcome and quality of life endpoint, analyses will be conducted in the ITT Analysis Set. Available data will be used; there will be no substitutions for missing data.

The QOL-B includes domains for physical functioning, role functioning, vitality, emotional functioning, social functioning, treatment burden, health perceptions and respiratory symptoms. For each domain, scores will be standardized on a 0 to 100 scale. Descriptive statistics for each domain at baseline and each visit will be presented by treatment group. The change from baseline to each visit will be analyzed using an analysis of covariance (ANCOVA) and the least squares (LS) mean, standard error (SE) of the LS mean and 2-sided 95% CI for the LS mean will be provided for each treatment group. The difference in LS means between treatment groups, 2-sided 95% CI and p-value will also be provided.

For the SGRQ, the global score and score for each component (symptoms, activity, and impacts) will be determined. Descriptive statistics for the global score and each component score at each visit will be presented by treatment group. The change from baseline to each visit will be analyzed using an ANCOVA, and the LS mean, and 2-sided 95% CI for the LS mean will be provided for each treatment group. The difference in LS means between treatment groups, 2-sided 95% CI and p-value will also be provided.

For the PROMIS Fatigue 7a Short Form, raw scores are converted to a standardized score. Descriptive statistics for the standardized score at baseline and each visit will be presented by treatment group. The change from baseline to each visit will be analyzed using an ANCOVA, and the LS mean, SE of the LS mean, and 95% CI for the LS mean will be provided for each treatment group. The difference in LS means between treatment groups, 95% CI and p-value will also be provided.

For the PGI-S, the number and percentage of subjects with each response will be presented by visit and treatment group. The PGI-S will also be categorized as mild/not present vs. moderate/severe and the number and percentage of subjects in each category will be presented by visit and treatment group. Exact 2-sided 95% CIs using the Clopper-Pearson method for the percent improved and a p-value from Fisher's exact test will be provided.

For the PGI-C, the number and percentage of subjects with each response will be presented by visit and treatment group. The PGI-C will also be categorized as improved vs. no change/worse and the number and percentage of subjects in each category will be presented by visit and treatment group. Exact 2-sided 95% CIs using the Clopper-Pearson method for the percent improved and a p-value from Fisher's exact test will be provided.

Descriptive statistics for severity of illness from the CGI change from baseline for each visit will be presented by treatment group. Descriptive statistics of the global improvement and the efficacy index from the CGI will also be provided by treatment group for each visit. A p-value from the Wilcoxon rank sum test for each outcome will also be presented.

At each visit based on the NTM Symptom Assessment Questionnaire, the number and percentage of subjects with a new symptom (compared with baseline) with severity worse than mild and no new symptoms with a severity worse than mild will be summarized by treatment group. Shift tables from baseline for each symptom at each visit will also be provided.

12.5.2.2 Microbiological Response

The number and percentage of subjects with a decrease in the mycobacterial load will be determined by treatment group at Day 84 in the ITT Analysis Set. Exact 2-sided 95% CIs for the point estimate of the percentage of subjects of subjects with a decrease in mycobacterial load in each treatment group will be determined using the Clopper-Pearson method. The odds ratio (omadacycline relative to placebo) and p-value will be calculated using Cochran-Mantel-Haenszel test, stratified by prior antibiotic use.

Kaplan-Meier methods will be utilized to determine the time to growth in liquid media only and time to first negative sputum culture in the ITT Analysis Set. Time to growth in liquid medium only will be defined as the number of days from the date of test article administration to the date of the first assessment where growth is detected in liquid medium only. Time to first negative sputum culture is defined as the number of days from the date of test article administration to the date of the first negative sputum culture. Subjects who died, withdrew, or took alternative antibiotic therapy for treatment of the NTM infection prior to growth in liquid medium only or negative sputum will be censored at the date of the death, study withdrawal, or the start date of the alternative antibiotic therapy respectively. The median, 25^{th} and 75^{th} percentile for time to growth in liquid media and time to first negative sputum culture will be provided with 2-sided 95% CIs. A p-value will be determined using a log-rank test.

12.6 Safety Endpoint(s)

All safety data will be analyzed in the Safety Analysis Set. Adverse events will be coded using the Medical Dictionary of Regulatory Activities. The incidence of treatment-emergent adverse events will be presented by system organ class (SOC) and preferred term (PT), by SOC, PT and relationship to test article, and by SOC, PT and severity. Serious AEs and treatment-emergent adverse events that lead to discontinuation of the test article will also be presented by SOC and PT. Descriptive statistics for clinical laboratory, vital signs, and ECG parameters, including change from baseline, will be presented by timepoint collected and for the overall most abnormal post-baseline value (for clinical laboratory and vitals sign parameters). Incidences of potentially clinically significant clinical laboratory results, vital signs and ECG parameters as defined in the SAP, will also be summarized by timepoint collected and the overall most abnormal post-baseline value (for clinical laboratory and vital sign parameters).

12.7 Data Monitoring Committee

Given the exploratory nature of this Phase 2 study using a product with a well-established safety profile, a data monitoring committee will not be utilized for this study.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable solution including but not limited to storage for all study-related documents. Regulatory agencies will be notified with the appropriate documentation.

An updated Form FDA 1572 will be filed with the sponsor for any changes in the study personnel reported in the current Form FDA 1572.

13.2 Institutional Review Board or Independent Ethics Committee Approval

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC/REB must be given to the sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor, monitors, auditors, designated agents of the sponsor, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

13.3 Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US 21 Code of Federal Regulations, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

13.4 Patient Information and Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent;
- Be given time to ask questions and time to consider the decision to participate;
- Voluntarily agree to participate in the study;
- Sign and date an IRB/IEC/REB approved-ICF.

13.5 Direct Access, Data Handling, and Record Keeping

13.5.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

13.5.2 Sponsor

The data are entered into an electronic database via eCRFs. The sponsor medical monitor reviews the data for safety information. The data are reviewed for completeness and logical consistency. Automated validation checks identify missing data, out-of-range data, and other data inconsistencies. The central safety and microbiology data will be processed electronically. Requests for data clarification are forwarded to the study site for resolution.

13.6 Protocol Adherence

13.6.1 Violations/Deviations

Investigators will agree to apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its agents to request approval of a prospective protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment and it cannot be implemented unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

13.6.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the

protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

13.7 Subject Injury

In general, subject to specific provisions in the clinical study agreement (CSA), if a subject is injured as a direct result of a test article, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

13.8 Pre-study Documentation

The investigator must provide the sponsor with the following documents before enrolling any subjects:

- Completed and signed Form FDA 1572 or equivalent.
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae and medical license (as applicable) for the investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on the Form FDA 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC/REB approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC/REB. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC/REB must also be provided to the sponsor.
- Copy of the IRB/IEC/REB-approved informed consent document to be used.
- Where applicable, a list of the IRB/IEC/REB members and their qualifications, and a description of the committee's working procedure.
- Copy of the protocol sign-off page signed by the investigator.
- Fully executed CSA.
- Where applicable, a financial disclosure form.
- A written document containing the name, location, certification number, and date of certification of the laboratories to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor must be notified if normal values or units of measurement change.

13.9 Retention of Data

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (a) 2 years after the last marketing authorization for the investigational test article has been approved or the sponsor has discontinued its research with respect to such investigational test article or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of its intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

13.10 Publication and Disclosure Policy

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical study results.

Upon completion of the study, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The institution and principal investigator (PI) shall not publish or present data from an individual study center until the complete multi-center study has been presented in full or for 2 years after the termination of the multi-center study, whichever occurs first. Subsequent publications must refer to the multi-center findings. Thereafter, if the PI expects to participate in the publication of data generated from this site, the institution and PI shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The PI shall act in good faith upon requested revisions, except that the PI shall delete any confidential information from such proposed publication. The PI shall delay submission of such publication or presentation materials for up to an additional 90 days to have a patent application(s) filed.

14 REFERENCE LIST

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Appendix 1 Schedule of Assessments

Study Phase	**Screening**	**Double-Blind Treatment**					**Follow-up**
Visit Name	**Screening[a]**	**Day 1 Baseline[b]**	**Day 14 Tele-visit[c]**	**Day 28**	**Day 56**	**Day 84/EOT**	**30 Day Safety Follow-up Call[d]**
Visit Window	**N/A**	**N/A**	**± 2d**	**± 3d**	**± 3d**	**+5d /- 2d**	**+ 7d**
Informed consent[e]	X						
Inclusion/exclusion criteria	X	X					
Medical history/current medical conditions	X						
Demography	X						
Physical examination	X					X	
Height	X						
Weight	X	X		X	X	X	
BMI	X						
Serum or urine pregnancy test[f]	X	X		X	X	X	
Vital signs (BP, HR, body temperature, and pulse oximetry)[g]	X	X		X	X	X	
Hematology[h]	X	X		X		X	
Serum chemistry	X	X		X		X	
Biomarkers (serum, plasma)[i]		X				X	
Sputum collection for microbiology[j]	X[k]	X		X	X	X	
CT scan of chest	X[l]					X	
12-lead ECG	X					X	
NTM Symptom Assessment Questionnaire	X	X		X	X	X	
St. George's Respiratory Questionnaire (SGRQ)		X		X	X	X	

Study Phase	**Screening**	**Double-Blind Treatment**					**Follow-up**
Visit Name	**Screening[a]**	**Day 1 Baseline[b]**	**Day 14 Tele-visit[c]**	**Day 28**	**Day 56**	**Day 84/EOT**	**30 Day Safety Follow-up Call[d]**
Visit Window	**N/A**	**N/A**	**± 2d**	**± 3d**	**± 3d**	**+5d /- 2d**	**+ 7d**
Quality of Life – Bronchiectasis (QOL-B)		X		X	X	X	
PROMIS-Fatigue Short Form 7a		X		X	X	X	
Patient Global Impression – Severity (PGI-S)		X		X	X	X	
Patient Global Impression – Change (PGI-C)				X	X	X	
Clinical Global Impression – Severity of Illness (CGI-S)		X		X	X	X	
Clinical Global Impression - Global Improvement Scale (CGI-I)				X	X	X	
Dispense test article		X		X	X		
Test article administration[m]		X ◄	———	———	———	► X	
Test article accountability and compliance				X	X	X	
Adverse events[n]	X	X	X	X	X	X	X
Prior/concomitant medications[o]	X	X	X	X	X	X	X

β-hCG = serum β-human chorionic gonadotropin; BMI = body mass index; BP = blood pressure; CT = computed tomography; d = day(s); ECG = electrocardiogram; eCRF = electronic case report form; EOT = end of treatment; HR = heart rate; ICF = informed consent form; MABc = *Mycobacterium abscessus* complex; MAC = *Mycobacterium avium* complex; N/A = not applicable; NTM = nontuberculous mycobacterial

a. Screening period may occur for up to 8 weeks prior to randomization to allow for sputum microbiology results. Screening procedures may occur on separate days. Subjects may be randomized as soon as all screening procedures have been performed and results have been received to verify eligibility criteria.
b. All Day 1/Baseline Visit procedures should be completed prior to subject dosing.
c. Day 14 visit will be performed remotely via telephone to assess safety.
d. A Safety Follow-up call will be performed 30-37 days after the subject's last dose of test article. At the investigator's discretion, the safety follow-up can be an office visit.
e. Written and signed ICF must be obtained before any study-related assessment is performed.
f. All female subjects will have a local urine or serum pregnancy test at Screening and at the Baseline Visit. Results will be used to confirm eligibility. In addition, blood will be collected for a serum β-hCG pregnancy test to be sent to the Central Laboratory at the Day 28 and Day 84/EOT visits. At Day 56

visit, a local urine or serum β-hCG pregnancy test may be performed. If Day 56 local pregnancy test results are positive, a serum β-hCG pregnancy test will be sent to the Central Laboratory for confirmation.

g. Vital signs should be captured after at least 5 minutes (+ 5 minutes) of rest while in a non-standing position (supine or sitting). Subsequent vital sign measurements should be captured in the same non-standing position.
h. Hematology includes coagulation.
i. Serum and plasma for biomarkers will be collected and stored for future use for all subjects who agree to provide samples during the consenting process.
j. Specimens may be obtained via spontaneous sputum expectoration or sputum induction. Approximately 5 mL of sputum should be collected per sample. To improve the probability of obtaining a good sputum specimen, at least 2 and preferably 3 spontaneously expectorated sputum samples will be obtained from subjects at each timepoint. Specimens should be collected by the subject on 2 to 3 consecutive days (when possible), just prior to, and up through the day of the scheduled study visit. If a subject is unable to produce sputum spontaneously and independently, sputum induction may be performed by appropriately qualified site staff to obtain one induced sputum specimen.
k. To be eligible for participation, subjects must have at least 1 prior positive culture for MABc in the 6 months prior to Screening, and 1 positive culture at Screening (note: the prior cultures and Screening cultures must be at least 30 days apart). At least 2 and preferably 3 spontaneously expectorated sputum samples (approximately 5 mL each) should be collected on 2 to 3 consecutive days (when possible) during the week following the subject signing informed consent.
l. May utilize results of chest CT scan performed within 3 months prior to Screening to determine eligibility (radiographic evidence of MABc infection). If no CT scan was obtained within prior 3 months, CT scan to be performed at Screening. High resolution CT scan is preferred, if available.
m. All doses will be taken orally, once daily in a fasted state. Fasting is defined as no food, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) or drink except water for at least 4 hours before dosing. After dosing, no food for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.
n. Adverse events will be reported and recorded from signing of ICF through the Follow-up call.
o. All antibiotics administered for the subject's MABc or MAC infection within 2 years prior to the date of informed consent will be recorded in the eCRF. All significant non-pharmacological therapies related to MABc infection including patient education, airway clearance technique, inspiratory muscle training and exercise training administered from 30 days prior to date of informed consent, and administered throughout the duration of the study through the 30-day follow-up period, will be recorded in the eCRF. All pharmacological therapies (regardless of indication) that have been administered from 7 days prior to the date of informed consent and administered throughout the duration of the study through the 30-day follow-up period, will be recorded in the eCRF. All significant non-pharmacological therapies not related to MABc infection administered from 7 days prior to date of informed consent, and administered throughout the duration of the study through the 30-day follow-up period, will be recorded in the eCRF.

Appendix 2 Equations and Conversion Factors

1. Cockcroft-Gault equation to calculate creatinine clearance (relevant to Exclusion Criterion number 6):

$$\frac{(140\text{-age [yrs]}) * \text{weight (kg)} * (Z)}{\text{Cr (mg/dL)} * 72}$$

Z = 1.0, if Male
Z = 0.85, if Female

2. Corticosteroid conversions (relevant to Exclusion Criterion number 5):

	Approximate equivalent dose[a] (mg)	Relative glucocorticoid activity	Relative mineralocorticoid activity	Duration of action (hours)
Glucocorticods				
Short-acting				
Hydrocortisone	20	1	1	8-12
Cortisone	25	0.8	0.8	8-12
Intermediate-acting				
Prednisone	5	4	0.8	12-36
Prednisolone	5	4	0.8	12-36
Methylprednisolone	4	5	Minimal	12-36
Triamcinolone	4	5	0	12-36
Long-acting				
Dexamethasone	0.75	30	Minimal	36-72
Betamethasone	0.6	30	Negligible	36-72
Mineralocorticoids				
Fludrocortisone	[b]	10-15	125-150	12-36

[a] Equivalent dose shown is for oral or IV administration. Relative potency for intra-ocular or intramuscular administration may vary considerably.

[b] Glucocorticoid doses which provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone are: prednisone or prednisolone 50 mg, or hydrocortisone 20 mg.

Source: Liu 2013

Appendix 3 Sputum Induction Guidelines

Introduction

Collection of adequate sputum samples (approximately 5 mL) is critical. Sputum samples will be collected by the subject (at home) and/or at the study site. In the event the subject is unable to spontaneously expectorate the required volume of sputum, induction may be performed at the study site by qualified site staff. This guidance document is intended to provide recommendations for obtaining an adequate sputum sample via sputum induction.

Recommended Equipment

- Standard handheld nebulizer – thoroughly cleaned and disinfected
- Sputum specimen containers with labels
- Sputum collection tubes (provided by the Central Laboratory)
- Hypertonic sodium chloride solution (at minimum 3%, plus 5% and 7% if needed)
- Other clinic supplies (eg, disinfectant/germicidal/alcohol wipes, gloves, masks, tissues, paper towels, etc.)

CONTRAINDICATIONS TO SPUTUM INDUCTION

- This procedure should not be performed in subjects in which severe coughing may be harmful, such as subjects with:
  - Recent or recurrent hemoptysis
  - Acute respiratory distress
  - Acute hypoxia (SaO_2 in room air of < 90%)
  - Known pneumothorax
  - Rib fractures or chest wall musculoskeletal injury
  - Unstable cardiac conditions
  - Recent eye surgery

Instructions:

Preparation

- Subjects should be instructed not to eat at least 1 hour prior to sputum induction.
- Subjects should be informed of the purpose of this procedure before commencing.
- The procedure should be discussed with the subject:
  - They will experience a salty taste in their mouth
  - They may cough
  - They will likely produce lung secretions that they will need to expectorate
  - If they have pre-existing hyperreactive airways eg, asthma, they will receive pre-medication with an inhaled bronchodilator
- Sputum induction should occur in a private, contained room, following clinic processes to ensure sterilization and prevent contamination.
- Site staff performing induction should wear gloves and an N95 mask for the duration of the procedure.

- All collection containers should have a sputum collection label completed with subject identifiers (ie: subject #, visit ID, collection date and time).
- The induction procedure should start with using lower concentrations of saline (eg, 3%) as per the investigator's discretion. Approximately 3-6 mL of hypertonic saline should be placed in the nebulizer.
- Subjects should be sitting up or in a semi-fowler position.

Nebulization

- Nebulization time is approximately 10 minutes in total, with breaks in nebulization at 5-minute intervals or if the patient has respiratory distress, excessive coughing.
- Nebulization may extend to 15 minutes if the patient is in no distress and more sputum needs to be collected.
- Nebulization should stop at 15 minutes total time, even if inadequate sputum is collected.
- The saline concentration may be increased to a maximum of 7% per investigator discretion.
- Subjects should be instructed to breathe slowly and deeply (pausing at peak inspiration) through the nebulizer mouthpiece inhaling the saline mist.
- If the subject needs to expectorate during nebulization, turn off the nebulizer and allow the subject to expectorate into the container.
    - If a sufficient specimen is collected, procedure can stop.
    - If an insufficient volume of sputum is collected, the subject should resume the nebulization treatment and complete the full 15-minute duration in three 5-min intervals.
- Subjects should be encouraged to blow their nose as needed during the induction to help prevent nasal secretions from becoming mixed with the sputum specimen.
- Upon completion, subjects should take a few deep breaths, swallow the extra saliva in their mouth and attempt to forcefully cough up a sputum sample into a sputum container. The container should be closed immediately after the appropriate volume of sputum (approximately 5 mL) is collected.
- Closely monitor the subject for tolerability issues or side effects.
- The sputum sample should be refrigerated until it is sent to the central specialty microbiology laboratory.
- Please refer to the Central Laboratory Manual for further instructions on packaging and shipping specimens to the lab.

Appendix 4 NTM Symptom Questionnaires

NTM Symptom Assessment Questionnaire – Baseline (Day 1) Visit

PART 1:

Instructions: Please indicate if you have experienced any of the following twelve symptoms within the past 7 days by using the scale below (Absent, Mild, Moderate or Severe). Please rate your **overall** impression of each symptom within the past 7 days. **Please circle one response for each symptom.**

SYMPTOM				
Cough	ABSENT	MILD	MODERATE	SEVERE
Coughing up blood	ABSENT	MILD	MODERATE	SEVERE
Wheezing	ABSENT	MILD	MODERATE	SEVERE
Chest pain	ABSENT	MILD	MODERATE	SEVERE
Throat clearing	ABSENT	MILD	MODERATE	SEVERE
Mucus (sputum) production	ABSENT	MILD	MODERATE	SEVERE
Shortness of breath	ABSENT	MILD	MODERATE	SEVERE
Fatigue	ABSENT	MILD	MODERATE	SEVERE
Fever	ABSENT	MILD	MODERATE	SEVERE
Night sweats	ABSENT	MILD	MODERATE	SEVERE
Poor appetite	ABSENT	MILD	MODERATE	SEVERE
Weight loss	ABSENT	MILD	MODERATE	SEVERE

PART 2:

Instructions: From the list of symptoms above, please indicate up to (3) symptoms which are most bothersome for you by ranking in order from most bothersome (#1) to least bothersome (#3).

1. _____

2. _____

3. _____

NTM Symptom Assessment Questionnaire – All Other Visits

Please indicate which visit the questionnaire is being completed at:

- ☐ Screening
- ☐ Day 28 Visit
- ☐ Day 56 Visit
- ☐ Day 84 Visit

Instructions: Please indicate if you have experienced any of the following twelve symptoms within the past 7 days by using the scale below (Absent, Mild, Moderate or Severe). Please rate your **overall** impression of each symptom within the past 7 days. **Please circle one response for each symptom.**

SYMPTOM				
Cough	ABSENT	MILD	MODERATE	SEVERE
Coughing up blood	ABSENT	MILD	MODERATE	SEVERE
Wheezing	ABSENT	MILD	MODERATE	SEVERE
Chest pain	ABSENT	MILD	MODERATE	SEVERE
Throat clearing	ABSENT	MILD	MODERATE	SEVERE
Mucus (sputum) production	ABSENT	MILD	MODERATE	SEVERE
Shortness of breath	ABSENT	MILD	MODERATE	SEVERE
Fatigue	ABSENT	MILD	MODERATE	SEVERE
Fever	ABSENT	MILD	MODERATE	SEVERE
Night sweats	ABSENT	MILD	MODERATE	SEVERE
Poor appetite	ABSENT	MILD	MODERATE	SEVERE
Weight loss	ABSENT	MILD	MODERATE	SEVERE

Appendix 5 Sponsor Signature

Study Title:	A Phase 2, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Omadacycline in Adult Subjects with Nontuberculous Mycobacterial (NTM) Pulmonary Disease Caused by *Mycobacterium abscessus* complex (MABc)
Study Number:	PTK0796-NTM-20203
Protocol Version 2.0 Final Date:	06-Dec-2021

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: [redacted]

[redacted]

VP, Medical and Scientific Strategy

Appendix 6 Investigator's Signature

Study Title:	A Phase 2, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Omadacycline in Adult Subjects with Nontuberculous Mycobacterial (NTM) Pulmonary Disease Caused by *Mycobacterium abscessus* complex (MABc)
Study Number:	PTK0796-NTM-20203
Protocol Version 2.0 Final Date:	06-Dec-2021

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Investigator Name:_____

Investigator Title:_____

Investigator Affiliation:_____

Investigator Address:_____

Investigator Phone Number:_____