Statistical Analysis Plan

Paratek Pharmaceuticals

PTK0796-NTM-20203

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)

Protocol Version: Protocol Version 2.0 (06 December 2021)

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Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ICE	intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	intent-to-treat
LS	least squares
MABc	mycobacterium abscessus complex
MAC	mycobacterium avium complex
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
NTM	nontuberculous mycobacterial
OR	odds ratio
PCS	potentially clinically significant
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PP	per-protocol
PROMIS	Patient-reported Outcomes Measurement Information System
PT	preferred term
QC	quality control
QOL-B	Quality of Life – Bronchiectasis
QTc	corrected QT interval
QTcF	corrected QT interval according to Fridericia's formula
SAP	statistical analysis plan
SGRQ	St Georges Respiratory Questionnaire
SOC	system organ class
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TLFs	tables, listings, and figures
WHO	World Health Organization

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Study PTK0796-NTM-20203 (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]). The purpose of this statistical analysis plan (SAP) is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol, version 2.0, 06-Dec-2021
- Annotated electronic case report form (eCRF), version 2.0, 01Feb2022.

3. STUDY OBJECTIVES

3.1 Primary Objectives

Efficacy: To evaluate the efficacy of omadacycline in adult subjects with NTM pulmonary disease caused by MABc based upon subject assessment of symptoms.

Safety: To evaluate the safety and tolerability of omadacycline in adult subjects with NTM pulmonary disease caused by MABc.

3.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate patient-reported outcomes and quality of life in adult subjects with NTM pulmonary disease caused by MABc
- To evaluate the microbiological response of omadacycline in adult subjects with NTM pulmonary disease caused by MABc

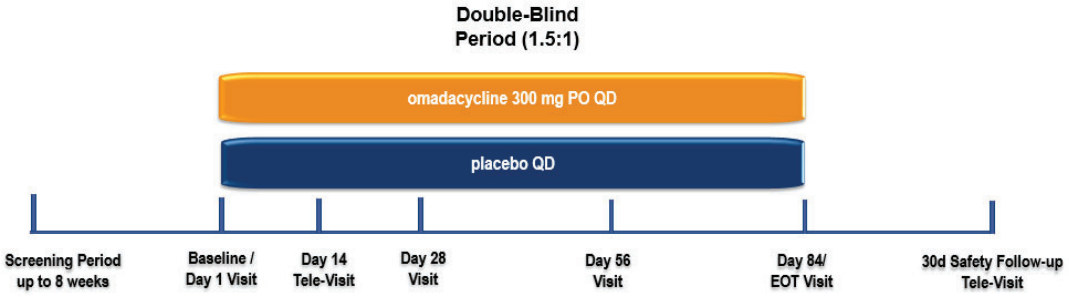
4. STUDY DESIGN AND PLAN

This is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicenter 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 (See Figure 1).

Figure 1. Study schema, protocol amendment v2.0, 06-Dec-21



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).

5. 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. 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 .05.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all p-values will be 2-sided. No adjustments for multiplicity will be made in this study, and any p-values presented are not testing pre-specified inferential hypotheses.

Continuous variables will be summarized by presenting the number of observations, means, SDs, medians, minimums, and maximums. Other summaries (e.g., quartiles, 5%, 95% CIs) may be used as appropriate.

Categorical variables will be summarized by presenting counts and percentages of subjects in corresponding categories. All possible categories as defined in the eCRF should be populated, even if they have zero counts. Percentages are based on the total number of subjects (N) for a given treatment and population, unless otherwise specified.

All summary tables will be presented by treatment group. Baseline summaries will also include a total summary column.

Individual subject data obtained from the eCRFs, external vendors, central clinical laboratory, central electrocardiogram (ECG) laboratory, and selected derived data will be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined before breaking the blind.

Any analyses performed after breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® statistical software, version 9.4 or higher (SAS Institute Inc). TLFs will be presented in rich text format (RTF) and/or PDF.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS Programming Quality Control". Study-specific QC requirements can be found in APPENDIX B: SAS PROGRAMMING QUALITY CONTROL REQUIREMENTS.

7. NOTATION OF TREATMENT GROUPS AND VISITS

Table 7.1.1 Notation of Treatment Groups

The following notation of treatment groups will be used throughout the report:

Full notation (as used in the study protocol)	Notation used throughout all tables, listings, and figures
300 mg oral omadacycline	Omadacycline 300 mg
Placebo	Placebo

Table 7.1.2 Visit Terminology

Visit	Notation used throughout all tables, listings, and figures
Screening	Screening
Day 1 Baseline	Day 1 (in Listings)/ Baseline (in Tables and Figures)
Day 14 Tele-visit (± 2d)	Day 14
Day 28 (± 3d)	Day 28

Day 56 (± 3d)	Day 56
Day 84 (+5d/-2d)	Day 84
EOT: defined as the visit occurring when subjects prematurely discontinue treatment (End of Treatment) (+5d/-2d)	EOT (shown on listings)
Day 84/EOT: defined as Day 84 for subjects who complete treatment or the visit occurring when subjects prematurely discontinue treatment (End of Treatment) (+5d/-2d)	Day 84/EOT (shown on tables)
30 Day Safety Follow-up Call (+7d)	Follow-up

EOT = end of treatment

For by visit summaries, the nominal visit will be summarized. If there is no nominal visit result, unscheduled visits that occur in the protocol defined window will be summarized instead. If multiple unscheduled visits occur in the window, the one closest to the nominal visit date will be used. For sputum cultures, if there are multiple positive cultures on the same day with different MICs to omadacycline, the culture with the highest MIC to omadacycline is used.

Study days corresponding to measurements are calculated as:

- Assessment date – date of first exposure to treatment + 1 (if assessment date is on or after the date of first exposure to treatment)
- Assessment date – date of first exposure to treatment (if assessment date is before the date of first exposure to treatment)

If the date of first exposure to treatment is missing, study days will be calculated by using the randomization date.

8. ANALYSIS SETS

The following subject population will be used for safety analyses:

- The safety analysis set will include all subjects who received at least 1 dose of test article. Treatment assignment will be based on the actual test article received the majority of time while on treatment.

The following subject populations will be used for efficacy analyses:

- The intent-to-treat (ITT) analysis set will include all randomized subjects. Treatment assignment will be based on the randomized treatment.
- The per-protocol (PP) analysis set will include 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. The decision whether a subject is excluded from the PP analysis set will be made prior to database lock and unblinding. Treatment assignment will be based on randomized treatment.

9. STUDY CONDUCT

9.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment group and overall. The number and percentage of subjects who are screened, randomized, subjects in each analysis set for all subjects and the number and percentage of subjects who complete treatment, subjects who prematurely discontinued test article and the reason for discontinuation, the number and percentage of subjects who complete the study 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.

A listing of all subjects who prematurely discontinued from test article and the reasons for discontinuation and all subjects who prematurely discontinued from the trial and the reasons for discontinuation will be presented.

9.2 Protocol and Good Clinical Practice (GCP) Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the Investigator, site personnel, or the subject. GCP deviation is any breach from GCP standards due to various reasons, including human error, technical glitches, or unforeseen circumstances.

Major protocol and GCP deviations are a subset of protocol and GCP deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

All protocol and GCP deviations, including the deviation designation (major or minor), category, and indication of whether the deviation led to an exclusion of a subject from the PP analysis set, will be presented in a data listing.

The number and percentage of subjects with any protocol and GCP deviation, with at least one minor, and with at least one major deviation will be summarized by treatment group in the ITT analysis set. Major protocol deviations will also be summarized by deviation category and treatment group in the ITT analysis set.

9.3 Eligibility

A listing of subjects in the ITT analysis set not fulfilling any eligibility criteria will be provided.

9.4 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification and preferred names using the WHO Drug Global dictionary B3 format, version March 2021.

Partial dates will be imputed. For details on imputation rules, refer to Appendix A: Presentation of Data and Programming Specifications. Imputed dates are only used for classification of a medication as a prior or concomitant medication; no other calculation, such as durations, will be done.

Prior medications are defined as any medication with a start date before the start date of test article. Concomitant medications are defined as any medication that was started before the start date of test article and with a stop date on or after the start date of test article or are considered ongoing, or that are started on or after the start date of test article. Medications can be considered both prior and concomitant. If the medication cannot be classified as a prior or concomitant medication, the medication will be considered as concomitant.

Medications will be summarized for each treatment group by level 4 ATC class (where applicable) and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class (where applicable) and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending subject count in the total column by ATC level (where applicable) and preferred name. The following summaries will be provided:

- Prior antibiotics administered for MABc or MAC pulmonary disease in the ITT and Safety analysis sets
- Concomitant antibiotics administered for MABc or MAC pulmonary disease from the last dose of test article through the date of the end of the study in the ITT and Safety analysis sets
- Prior medications other than antibiotics administered for MABc or MAC pulmonary disease in the Safety analysis set
- Concomitant medications other than antibiotics administered for MABc or MAC pulmonary disease in the Safety analysis set.

10. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

10.1 Demographics, Medical History and NTM Assessment

Demographics, baseline characteristics, medical history, and baseline assessment of NTM will be summarized by treatment group and overall.

The NTM Symptom Assessment Questionnaire asks subjects to rank the top three most bothersome symptoms on the scale at the baseline visit. Each symptom will be scored with 3 points for a top rating, 2 points for a second-place rating, and 1 point for a third place-rating. Each symptom will be summed within treatment group and this sum will be presented on the baseline characteristics table with the symptom having the highest overall sum across treatment

groups appearing first to the symptom with the lowest score appearing last. This will be referred to as the NTM Baseline Symptom Bothersome Ranking.

The following demographic and baseline characteristics will be summarized for the ITT analysis set (except where indicated):

- Baseline demographics and characteristics: age as a continuous variable, age categorized as ≤ 65 and > 65 years, sex, ethnicity, race, height (cm), weight (kg), body mass index (BMI) (kg/m^2), by treatment group and overall. Baseline demographics and characteristics will be summarized for the ITT and safety analysis sets.

- The number and percentage of subjects in each randomization stratum (received prior treatment for NTM, did not receive prior treatment for NTM) based on the prior antibiotic data from the CRF will be presented by treatment group and overall. The table will also present the number and percentage of subjects with each severity category (absent, mild, moderate, severe) for the NTM symptoms at baseline from the NTM Symptom Questionnaire by treatment group and overall and in each randomization stratum. The Most Bothersome Symptom Ranking will also be presented by treatment group, overall and in each randomization stratum. The definition of the Most Bothersome Symptom Ranking is as the following. Subjects are asked to list up to 3 of their most bothersome symptoms at baseline. For each subject the number 1 mostly highly rated symptom will be given a score of 3, the second most highly rated will be given a score of 2, and the third most highly rated will be given a score of 1. Scores for each symptom will be tallied across all subjects. The symptom with the highest overall score will be considered most bothersome across the entire population, the second highest will be considered the second most bothersome for the entire population, etc..

- NTM disease history: duration of the MABc NTM pulmonary disease (defined as the number of days from the date of randomization to the first date of diagnosis of NTM pulmonary disease caused by MABc), if the subject had ever been diagnosed with NTM pulmonary disease caused by Mycobacterium avium complex (MAC), duration of NTM pulmonary disease caused by MAC (defined as the number of days from the date of randomization to the first date of diagnosis of NTM pulmonary disease caused by MAC), subjects with respiratory culture positive for MAC in the 6 months prior to screening, subjects having known chronic obstructive pulmonary disease (COPD), subjects having known bronchiectasis, the subject's smoking status (never smoked, former smoker and current smoker) and for former and current smokers, the length of smoking. For former smokers, length of smoking in years will be based on date started smoking to date stopped smoking + 1. For current smokers, length of smoking in years will be based on date started smoking to date of randomization + 1.

- Medical history: The verbatim term of the medical history condition/event will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0.

Medical history will be summarized by treatment group and overall in the ITT and Safety analysis sets. The summary will show the system organ class (SOC) and preferred term (PT) ordered by descending subject count in the total column. Subjects will only be counted once for each SOC and for each PT within SOC.

10.2 Microbiology

10.2.1 Selection of Sample for Analysis

Sputum samples are collected at Screening, Baseline/Day 1, Day 28, Day 56 and Day 84/EOT. At least 2 and preferably 3 sputum samples are obtained at each time point. 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.

The sputum specimens will be processed by a Central Specialty Microbiology Lab. 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*.

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.

Sputum samples noted to be of low volume will not be used for analysis unless all potential samples at a time point are of low volume. If all potential samples are of a low volume (signifying lower quality), the algorithms noted below for sample selection will be used.

For MIC susceptibility and outcome analyses of the MABc, the sample closest to but prior to the first dose of study drug (based on collection date and if on the same day as the first dose of study drug, collection date and time) which is positive for MABc is used as the baseline sample. If there are two samples positive for MABc with different subspecies, the one positive for *M. abscessus* subspecies *abscessus* is used. If multiple samples collected on the same day are positive for MABc, the sample positive for *M. abscessus* subspecies *abscessus* and with the highest MIC to omadacycline is considered the baseline sample. If the MICs are the same, the sample closest to the time of first dose of study drug based on time is used. The baseline samples for MAC and other species of mycobacterium (not *abscessus*) are defined in a similar manner and may or may not be the same sample as the one with MABc.

For post-baseline samples, a similar process is used for selecting the sample for analysis as that used for the baseline sample. The sample that is positive for MABc that is closest to the nominal/intended visit day should be selected.

10.2.2 Baseline Analyses

The following will be provided for the baseline MABc specimen:

- Baseline positive culture for MABc and by subspecies, as well as MAC and other mycobacterium.
- Distribution of the semi-quantitative score defined as follows:

Semi-quantitative culture scores	Growth in broth	Growth on agar plate	CFU/mL on an agar plate
0	-	-	0
1	+	-	0
2	+/-	+	1 - <50
3	+/-	+	50-99
4	+/-	+	100-199
5	+/-	+	200-299
6	+/-	+	≥300

- Distribution of MIC to amikacin, cefoxitin, ciprofloxacin, clarithromycin, clarithromycin-D14, clofazimine, doxycycline, imipenem, linezolid, minocycline, moxifloxacin, omadacycline, tigecycline, and trimethoprim/sulfamethoxazole
- Susceptibility profile (interpreted as resistant, susceptible and intermediate according to CLSI breakpoints) to each antibiotic with defined breakpoints
- Multidrug Resistance (MDR) defined as nonsusceptibility (MIC value interpreted as "I" or "R") to at least one agent in three or more antimicrobial categories. Agents that do not have susceptibility interpretations i.e. those in Table 10.3.2 with 'N/A/' will not be considered in this analysis.
- MIC range, MIC_{50} and MIC_{90} to omadacycline

Table 10.3.2. Antimicrobial Categories, Agents and CLSI Breakpoints

		MIC ug/mL		
Antimicrobial Category for MDR evaluation	**Antimicrobial Agent**	**S**	**I**	**R**
Aminoglycoside	Amikacin	≤16	32	≥64
Cephalosporin	Cefoxitin	≤16	32-64	≥128
Fluoroquinolone	Ciprofloxacin	≤1	2	≥4
Macrolide	Clarithromycin	≤2	4	≥8
N/A	Clofazimine	N/A	N/A	N/A
Tetracycline	Doxycycline	≤1	2-4	≥8
Carbapenem	Imipenem	≤4	8-16	≥32
Oxazolidinone	Linezolid	≤8	16	≥32

N/A	Minocycline	N/A	N/A	N/A
Fluoroquinolone	Moxifloxacin	≤1	2	≥4
Antifolate	Trimethoprim-sulfamethoxazole	≤2/38		≥4/76
N/A	Tigecycline	N/A	N/A	N/A

S=Susceptible, I=Intermediate, R=Resistant

Clinical and Laboratory Standards Institute. Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes 1st ed. CLSI document M62. 2018. CLSI, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania, 19087-1898, USA.

Microbiology results will be incorporated into several of the efficacy analyses, as defined in Section 11.1.

The by-subject listings noted below will also be provided. On each listing, all samples will be presented and the baseline and post-baseline samples selected as indicated above will be indicated with a flag.

- Decreasing susceptibility (defined as a greater than 4-fold increase in MIC to a given antimicrobial agent from the baseline sample to the post-baseline sample) at any visit. The listing will show the MICs for all antimicrobials, including those that do not show decreasing susceptibility
- Drug resistance markers at all visits
- Smear results at all visits
- Colony count data including CFU count and grouped CFU count (1-49, 50-100, >100-200, >200-500

A listing of MIC data for all samples will also be provided as will a listing of all other results for all samples.

11. EFFICACY ANALYSES

The primary and secondary efficacy analyses will be based on the ITT analysis set. Supportive efficacy analyses will be performed using the PP analysis set.

11.1 Efficacy Variables

The primary efficacy endpoints are:

- Clinical response (Definition 1) is defined as improvement at the Day 84 visit in severity of at least 50% of symptoms on the NTM Symptom Assessment Questionnaire present at baseline.

- Clinical response (Definition 2): is defined as improvement at the Day 84 visit in severity of at least 50% of symptoms on the NTM Symptom Assessment Questionnaire present at baseline and no deterioration in severity of any symptoms present at baseline.

Supportive analyses include analysis of clinical response (Definition 1 and Definition 2) at the Day 28 and Day 56 visits.

The secondary efficacy endpoints are:

- Change from baseline in Quality of Life - Bronchiectasis (QOL-B) domain scores at days 28, 56, 84, and Day 84/EOT
- Change from baseline in the St George's Respiratory Questionnaire (SGRQ) global and component scores at days 28, 56, 84, and Day 84/EOT
- Change from baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) Fatigue 7a Short Form standardized score at days 28, 56, 84, and Day 84/EOT
- The Patient Global Impression – Change (PGI-C) response at days 28, 56, 84, and Day 84/EOT
- The Patient Global Impression – Severity (PGI-S) response at days 28, 56, 84, and Day 84/EOT
- The Clinical Global Impression – Improvement (CGI-I) response at days 28, 56, 84, and Day 84/EOT
- The Clinical Global Impression – Severity (CGI-S) response at days 28, 56, 84, and Day 84/EOT
- The percentage of subjects with a new symptom (defined as a symptom present post-baseline but absent at baseline) on the NTM Symptom Assessment Questionnaire with severity worse than mild at days 28, 56, 84, and Day 84/EOT
- The percentage of subjects with a decrease in quantitative MABc sputum culture from baseline to Day 84
- Time to growth in liquid medium only
- Time to first sputum culture negative for MABc

The additional efficacy endpoints are:

- Time to detection of MABc in growth media at baseline and the Day 28, 56, 84 and Day 84/EOT visits
- The percentage of subjects who convert from a positive MABc sputum culture at baseline to a sputum culture negative for MABc at any time post-baseline and at the Day 28, 56, 84 and Day 84/EOT visits
- In those subjects whose first negative culture (i.e., convert from a positive MABc sputum culture at baseline to a negative MABc sputum culture) is on the Day 28, 56, 84 and Day

84/EOT visits, the number and percentage of subjects with a culture positive for *M. avium* or other non-abscessus mycobacterium species at baseline

- The percentage of subjects who convert from a positive MABc culture at baseline to a sputum culture negative for MABc post-baseline (through the Day 56 visit) and have no subsequent positive MABc sputum culture during the study
- The number and percentage of subjects who convert from a positive MABc sputum culture at baseline to a sputum culture negative for MABc or with MABc growth only in liquid medium at any time post-baseline and at the Day 28, 56, 84 and Day 84/EOT visits
- Quantitative mycobacterial load (CFU/mL) and semi-quantitative score of the MABc at baseline and the Day 28, 56, 84 and Day 84/EOT visits

11.2 Baseline Values

Unless otherwise noted, baseline is defined as the last non missing value recorded before the first dose of test article. Unscheduled visits will be used in the determination of baseline values, when applicable.

For microbiologic analysis, see Section 10.3.1 for determination of the baseline sputum sample.

11.3 Adjustments for Covariates

The model for the primary efficacy and some secondary efficacy analyses will include adjustments for randomization stratification factor:

- Prior treatment of NTM caused by MABc at baseline status (received prior antibiotic treatment for NTM vs did not receive prior treatment for NTM)

If the sample size is too small in one of the randomization stratification subgroups such that an adjusted analyses cannot be performed, unadjusted analyses will be used

11.4 Handling of Dropouts or Missing Data

Data imputation methods for the primary endpoint and other analyses for the primary endpoint are described in Section 11.1.

No imputations will be made for missing values for secondary endpoints. Summaries for these endpoints will be based on observed data only.

11.5 Interim Analysis and Data Monitoring

No interim analyses or data monitoring committee are planned for this study.

11.6 Examination of Subgroups

Subgroup analyses by prior treatment for NTM or baseline microbiological characteristics (e.g., MIC values) may be conducted if subgroup sample sizes are sufficient. This will be predetermined prior to database lock.

11.7 Multiple Comparison/Multiplicity

As the study is exploratory with respect to efficacy, no adjustments for multiplicity will be made in this study.

11.8 Multicenter Studies

This is multicenter study, with approximately 20 centers in the US participating. Approximately 75 subjects will be randomly assigned, leading to approximately 4 subjects per center.

The expected low number of subjects at some centers does not allow center to be included as a covariate in the statistical model.

12. METHODS OF EFFICACY ANALYSIS

12.1 Primary Efficacy Analyses

The study is exploratory with respect to efficacy determination. The study is designed to provide an initial assessment of efficacy rather than test a specific hypothesis. Efficacy will be evaluated based on endpoints defined by subject-reported NTM symptoms, subject-reported outcomes and quality of life measures, and microbiologic assessment. Nominal p-values will be provided as descriptive statistics.

12.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of clinical response at the Day 84 visit is defined in two ways as noted in Section 10.1. For Definition 1, clinical response is defined as the improvement in severity of at least 50% of symptoms on the NTM Symptom Assessment Questionnaire that were present at baseline at the Day 84 visit and for Definition 2 clinical response is defined as the improvement in severity of at least 50% of symptoms on the NTM Symptom Assessment Questionnaire that were present at baseline at the Day 84 visit and no deterioration in severity of any symptoms present at baseline. The NTM Symptom Assessment Questionnaire has 12 symptoms listed, however subjects may not be experiencing all symptoms at baseline. Therefore, the number of symptoms each subject has scored at least Mild severity at baseline will be counted and will serve as the denominator for this definition of improvement in severity of at least 50% of symptoms. For example, a subject with 6 symptoms scoring at least Mild severity at baseline would then be considered a responder in this analysis if they experienced improvement on at least 3 symptoms. A subject with 7 symptoms scoring at least Mild at baseline would require improvement on at least 4 symptoms. Symptoms which were not

present at baseline, or which increased in severity are not considered in Definition 1 of clinical response. For Definition 2, if any symptom present at baseline (i.e., not absent) worsens in severity at the Day 84 visit, the subject would be considered a non-responder. Symptoms which were not present at baseline are not considered in Definition 2 of clinical response. Clinical response (both definitions) will be dependent on the presence of intercurrent events (ICEs) as defined in Section 11.1.2. Subjects who discontinued from the trial early or who had a missing Day 84 assessment for some other reasons will be considered non responders in this analysis.

12.1.2 Estimand Framework for the Primary Efficacy Endpoint

In general, clinical response (both definitions) 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, withdraw from study treatment early, and/or die before reaching Day 84 will be considered as not achieving clinical response. Subjects with missing data at the Day 84 assessment will also be considered as not achieving clinical response.

As detailed in the ICH E9 (R1) addendum, the following 5 attributes will define the estimand framework for the primary endpoint (both definitions) and sensitivity analyses around the primary endpoint (both definitions). The primary estimand combines responses as assessed with a composite variable strategy for handling ICEs.

- Treatment condition: administration of omadacycline or placebo
- Population: ITT analysis set
- Endpoint: clinical response at Day 84
- Intercurrent events: ICEs are defined below.
- Population-level summary: between treatment group difference expressed in terms of an odds ratio

The following ICEs will be defined for the primary estimand and analysis:

- ICE-1: Subjects receiving alternative antibiotic therapy for NTM (not including chronic macrolides). This includes subjects who prematurely discontinue test article for any reason, including an adverse event, and receive alternative antibiotic therapy for NTM. Subjects with this ICE will be considered non-responders regardless of their Day 84 assessment for the primary analysis (Composite strategy).
- ICE-2: Subjects receiving chronic macrolides (starting prior to first dose of study drug). The Day 84 value for clinical response will be used regardless of the occurrence of this ICE (Treatment policy)
- ICE-3: Subjects who died prior to Day 84. Subjects with this ICE will be considered a non-responder for the primary analysis. (Composite strategy)
- ICE-4: Subjects who discontinue test article for any reason and do not receive an alternative antibiotic for NTM. Subjects with this ICE will be considered non-responders (Composite strategy).

Analyses will be conducted for both definitions of the primary endpoint. The number and percentage of subjects with a clinical response and without a clinical response will be presented.by treatment group for the ITT analysis set. Exact 2-sided 95% 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 (OR) (Omadacycline relative to Placebo) and p-value will be calculated using Cochran-Mantel Haenszel (CMH) test, stratified by prior antibiotic use. If the sample size is too small in one of the randomization stratification subgroups such that an adjusted analysis cannot be performed, an unadjusted analysis (chi-squared or Fisher's exact test) will be used.

12.1.3 Other Analyses for the Primary Efficacy Endpoint

The analyses described below will be performed for both definitions of the primary efficacy endpoint.

The primary analysis will be repeated for the PP analysis set.

A sensitivity analysis will also be done using the treatment policy for ICE-1 in the ITT analysis set. The Day 84 visit value for clinical response will be used regardless of subjects receiving alternative antibiotic therapy for NTM (not including chronic macrolides).

A subgroup analysis by the randomization stratification factor levels for the primary endpoint will also be conducted.

Clinical response Definitions 1 and 2 will also be analyzed at the Day 28 and Day 56 visits.

12.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be presented as collected. Missing data will not be imputed and no adjustment for ICEs will be performed. All secondary efficacy endpoints will be analyzed using the ITT analysis set. All secondary efficacy endpoints will be summarized using descriptive statistics at each scheduled time point by treatment group as described in Section 6.

The Day 84 visit time point will be presented with data as collected. The Day 84/EOT visit timepoint will include subjects who end treatment on Day 84 as well as subjects who prematurely discontinue treatment.

Secondary endpoints, where appropriate, will be analyzed using an analysis of covariance (ANCOVA) model at each visit which will include the change from baseline as the dependent variable and randomized treatment group and stratification factor (prior antibiotic treatment for MABc NTM) as fixed factors and corresponding baseline score as a covariate. Model estimated least squares (LS) means, their SDs, and 95% CIs will be presented. The difference in LS means, SDs, 95% CIs, and a p-value testing the difference between treatment group LS means will be provided.

12.2.1 Quality of Life – Bronchiectasis (QOL-B)

The first secondary efficacy endpoint is the change from baseline in the QOL-B domain scores at the Days 28, 56, and 84 visit, and Day 84/EOT. Descriptive statistics will be provided for each domain at each time point and ANCOVA estimates will be provided as described in Section 12.2. A graph of the cumulative distribution of the change from baseline to Day 84 for the respiratory domain by treatment group will also be provided.

12.2.2 St George's Respiratory Questionnaire (SGRQ)

The second secondary efficacy endpoint is the change from baseline in the SGRQ global and component scores at the Day 28, 56, and 84 visit, and Day 84/EOT. Descriptive statistics will be provided for the global score and each component score at each time point and ANCOVA estimates will be provided as described in Section 12.2.

12.2.3 Patient-reported Outcomes Measurement Information System (PROMIS)

The third secondary efficacy endpoint is the change from baseline in the PROMIS Fatigue 7a Short Form standardized score at the Day 28, 56, and 84 visit, and Day 84/EOT. Descriptive statistics will be provided for the standardized score at each time point and ANCOVA estimates will be provided as described in Section 12.2.

12.2.4 Patient Global Impression-Change (PGI-C)

The fourth secondary efficacy endpoint is the PGI-C assessed at the Day 28, 56, and 84 visit, and Day 84/EOT.

Subject response will also be categorized as subjects who experienced an improvement and those who did not experience improvement. The number and percentage of subjects in each category (improvement/no improvement) will be presented by treatment group along with exact 2-sided 95% CIs using the Clopper-Pearson method. The difference between treatment groups in percentages of subjects experiencing improvement will be presented along with a 2-sided 95% exact CI. The p-value from a Fisher's exact test will be provided.

12.2.5 Patient Global Impression-Severity (PGI-S)

The fifth secondary efficacy endpoint is the PGI-S response at the Day 28, 56, and 84 visit, and Day 84/EOT. The PGI-S will be analyzed similarly to the PGI-C as described in Section 12.2.4 except subject response will be grouped as subjects with responses of Not Present/Mild versus those with responses of Moderate/Severe. The difference between treatment groups in percentage of subjects with a response of Not Present/Mild will be presented along with a 2-sided 95% exact CI. The p-value from a Fisher's exact test will be provided.

An additional analysis of the PGI-S will summarize change from baseline as improved, no change and worsened at the Day 28, 56 and 84 visit, and Day 84/EOT. The number and percentage of subjects in each change category will be provided.

12.2.6 Clinical Global Impression-Improvement (CGI-I)

The sixth secondary efficacy endpoint is the CGI-I response at the Day 28, 56, and 84 visit, and Day 84/EOT. The number and percentage of subjects with each response will be presented by treatment group. The p-value from a Wilcoxon rank sum test will be provided.

An additional analysis of the CGI-I will summarize change from baseline as improved, no change and worsened at the Day 28, 56 and 84 visit, and Day 84/EOT. The number and percentage of subjects in each change category will be provided.

12.2.7 Clinical Global Impression-Severity (CGI-S)

The seventh secondary efficacy endpoint is the CGI-S response at the Day 28, 56, and 84 visit, and Day 84/EOT. The CGI-S will be analyzed similarly to the CGI-I described in Section 12.2.6.

12.2.8 Percentage of Subjects with a new Symptom

The eighth secondary efficacy endpoint is the percentage of subjects with a new symptom (compared to baseline) on the NTM Symptom Assessment Questionnaire with severity worse than mild at the Day 28, 56, and 84 visit, and Day 84/EOT.

For a symptom to be considered new it must be absent at baseline and graded with a severity worse than mild at the post-baseline assessment

The number and percentage of subjects with a new symptom worse than mild, with a new symptom that is not worse than mild, and no new symptom will be presented at each time point.

A shift table will also be provided for the shift from baseline severity to each post-baseline time point severity for each symptom.

12.2.9 Percentage of Subjects with a Decrease in Quantitative Mycobacterial Sputum

The ninth secondary efficacy endpoint is the percentage of subjects with a decrease in quantitative mycobacterial load from the sputum culture collected at the Day 84 visit and defined as a reduction in the semi-quantitative score (as defined in Table 10.3.2) as compared to baseline. The number and percentage of subjects with a reduction in the semi-quantitative score at the Day 84 visit will be presented for the ITT analysis set by treatment group. Exact 2-sided 95% CIs for the point estimate of the percentage of subjects with a decrease 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. If the sample size is too small in one of the randomization stratification subgroups such that an adjusted analysis cannot be performed, an unadjusted analysis (chi-squared or Fisher's exact test) will be used.

12.2.10 Time to Growth in Liquid Medium Only

Kaplan-Meier methods will be utilized to determine the time to growth in liquid medium only for MABc for the ITT Analysis Set by treatment group. The analysis will be limited to subjects with growth on agar plate at baseline 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. If there is no sputum sample indicating growth in liquid medium only but there is a negative culture (defined in Section 12.2.11), the date of the first negative culture will be used for the determination of time to growth in liquid medium only.

Subjects who died, withdrew from the study, or received alternative antibiotic therapy (not including chronic macrolides) for treatment of the NTM infection prior to growth in liquid medium only for MABc (or a negative culture, if no sputum sample indicating growth in liquid medium only) will be censored at the date of the death, study withdrawal, or the start date of the alternative antibiotic therapy respectively. Subjects who have a positive sputum culture (defined as growth in both liquid medium and agar plate [growth on both LJ slant and biplate]) through Day 84 will be censored at the date of the Day 84 visit.

The median, 25th and 75th percentile for time to growth in liquid medium only will be provided with 2-sided 95% CIs for each treatment group. A p-value will be determined using a stratified (by prior antibiotic use) log-rank test. Kaplan-Meier curve for time to growth in liquid medium only will be provided in a figure.

12.2.11 Time to First Negative Sputum Culture

Kaplan-Meier methods will be utilized to determine the time to first sputum culture negative for MABc for the ITT Analysis Set by treatment group. Time to first negative sputum culture is defined as the number of days from the date of the first dose of test article administration to the date of the first sputum culture negative for MABc. A culture is considered negative if there is no growth in broth (ie, liquid medium) and no growth on agar plate (ie, no growth on either LJ slant or biplate) for MABc regardless of subspecies. For example, if the baseline culture grows *M. abcessus* subspecies *abcessus* and the post-baseline sample grows *M. abcessus* subspecies *massiliense*, the culture is considered positive for MABc. Subjects who died, withdrew from the study, or received alternative antibiotic therapy (not including chronic macrolides) for treatment of the NTM infection prior to sputum culture negative for MABc will be censored at the date of the death, study withdrawal, or the start date of the alternative antibiotic therapy respectively. Subjects who have a positive sputum culture through Day 84 will be censored at the date of the Day 84 visit.

The median, 25th and 75th percentile for time to first negative sputum culture will be provided with 2-sided 95% CIs for each treatment group. The probability of a negative sputum culture at Days 28, 56 and 84 will also be presented along with the 2-sided 95% CIs for each treatment group. A p-value will be determined using a stratified (by prior antibiotic use) log-rank test. Kaplan-Meier curve for time to first negative sputum culture will be provided in a figure.

12.3 Additional Efficacy Analyses

- Time to detection of MABc (in days) in liquid growth medium at baseline and the Day 28, 56, 84 and Day 84/EOT visits will be summarized by treatment group, including n, mean, SDs, median, minimum and maximum.

- The number and percentage of subjects who convert from a positive MABc sputum culture at baseline to a sputum culture negative for MABc at any time post-baseline and at the Day 28, 56, 84 and Day 84/EOT visits and who do not convert to a negative culture (i.e., remain positive) will be summarized by treatment group.
- In those subjects whose first negative culture (i.e., convert from a positive MABc culture at baseline to a negative MABc culture) is on the Day 28, 56, 84 and Day 84/EOT visits, the number and percentage of subjects with a culture positive for *M. avium* or other non-abscessus mycobacterium species at baseline and at the visit will be summarized by treatment group.

- The number and percentage of subjects who convert from a positive MABc culture at baseline to a sputum culture negative for MABc by the Day 56 visit and have no subsequent positive MABc culture will be presented, as well as the number and percentage of subjects who convert to a negative culture by the Day 56 visit and have a subsequent positive culture, and those who do not convert to a negative culture by Day 56 will be summarized by treatment group.
- The number and percentage of subjects who convert from a positive MABc sputum culture at baseline to a sputum culture negative for MABc or growth of MABc only in liquid medium at any time post-baseline and at the Day 28, 56, 84 and Day 84/EOT visits and who do not convert to a negative culture will be summarized by treatment group.

- The number and percentage of subjects whose first negative culture (i.e., convert from a positive MABc culture at baseline to a negative MABc culture) is on the Day 28, 56, 84 and Day 84/EOT visits will be summarized by treatment group.

- A shift table of the semi-quantitative score from baseline to Days 28, 56, 84 and EOT visits will be presented by treatment group.

- Quantitative mycobacterial load (CFU/mL) and semi-quantitative score of the MABc at baseline and the Day 28, 56, 84 and Day 84/EOT visits will be summarized by treatment group, including including n, mean, SDs, median, minimum, and maximum, geometric mean, 95% CI of geometric mean, and %CV for mycobacterial load and number and percentage of subject of each semi-quantitative score.

- For each definition of the primary endpoint, the number and percentage of subjects with a clinical response and who had culture conversion (ie, converted from a positive MABc sputum culture at baseline to a negative sputum culture at the Day 84 visit), clinical response and did not have culture conversion, clinical nonresponse and had culture

conversion, and clinical nonresponse and did not have culture conversion, will be presented by treatment group.

- The cumulative distribution of the change from baseline to the Day 84 visit in the respiratory domain of the QOL-B by PGI-S (categorized as improved vs. no change/worsened) will be provided as a graph.

- Descriptive statistics of the change from baseline to the Day 84 visit in the respiratory domain of the QOL-B in subjects who converted from positive MABc sputum culture at baseline to a negative sputum culture at the Day 84 visit, by treatment group will be presented.

- A subject will be defined as a responder if all 3 of his/her most bothersome symptoms at baseline are absent or mild at the Day 84 visit and a non-responder if at least one of the most bothersome symptoms is worse than mild. The number and percentage of subjects defined as a responder and nonresponder will be presented by treatment group.

- A sample is considered positive if there was any growth in broth or agar. A sample is considered negative if there was no growth in broth and agar.

13. SAFETY ANALYSES

All safety analyses will be based on the safety analysis set.

13.1 Extent of Exposure

Test article exposure will be summarized for each treatment using the total number of doses taken, total dose received, and the duration of treatment. Subjects are prescribed to take 2 tablets once per day for the duration of the study.

Test article compliance will be calculated as follows:

- Compliance (%): (actual number of used tablets in total) / (number of prescribed tablets to be taken per the actual treatment period) × 100
- Actual number of used tablets: number of tablets dispensed – number of tablets returned
- Prescribed number of tablets to be taken: duration of test article administration (days) × 2 daily tablets
- Duration of test article administration (days) = date of last administration – date of first administration + 1

Test article compliance will be summarized by treatment group using counts and percentages as categorized below:

- >80%
- <=80%

In the event that data regarding the number of tablets "returned" is missing, the compliance calculation will ignore this interval in the calculation of compliance. For example, if a subject completes through Day 56 and is dispensed a final kit, but then is lost to follow up, the expected duration of administration will be calculated through the last dose date recorded on the kit returned at the Day 56 visit and the number of tablets taken will be based on the data from the first 2 kits. Similarly, if data regarding the number of tablets "returned" from the dosing interval between Day 28 and Day 56 is missing then the duration of dosing will be adjusted to remove this interval and the number of tablets taken will be based on recorded data from dosing intervals between Baseline and Day 28, and between Day 56 and Day 84.

13.2 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are defined as those AEs that occurred on or after first dose of test article and those existing AEs that worsened on or after first dose of test article. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such. Verbatim terms in the eCRFs will be mapped to SOCs and PTs using MedDRA, version 24.0.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PTs will be ordered by descending subject count in the total column by SOC and PT. Summaries of the following types will be presented:

- Overall summary of AEs that contains an overview of each of the following points
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs by MedDRA PT shown in order of descending frequency of PT in the omadacycline group
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. Adverse events with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA SOC, PT, and closest relationship to test article (related/not related) as classified by the principal investigator. At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs resulting in death by MedDRA SOC and PT

- Subject incidence of TEAEs leading to test article discontinuation by MedDRA SOC and PT
- Subject incidence of TEAEs leading to study discontinuation by MedDRA SOC and PT
- Subject incidence of TEAEs that occurred with onset date up through Day 15 by MedDRA SOC and PT
- Subject incidence of TEAEs that occurred with onset date after Day 15 by MedDRA SOC and PT

A summary of TEAEs experienced by treatment arm by PT will be provided.

Separate listings of serious AEs (SAEs), AEs resulting in death, AEs leading to test article discontinuation, and AEs leading to study discontinuation will be provided.

13.3 Clinical Laboratory Evaluation

Laboratory parameters (serum chemistry, hematology, and coagulation) will be summarized using descriptive statistics at baseline and at each post-baseline time point (the Day 28 and 84 visit, Day84/EOT) and for the most extreme (high and/or low) post-baseline value at any visit (including unscheduled results). Changes from baseline will also be summarized.

Select laboratory parameters will be graded according to the Division of Microbiology and Infectious Diseases (DMID) grading criteria, version 5.0. Incidence of potentially clinically significant (PCS) events (at least a 2-grade increase from baseline) will be presented by time point and for the most extreme post-baseline value at any visit (including unscheduled results).

The number and percentage (based on the number of subjects with a normal level at baseline) of subjects in each treatment group with an elevated transaminase (AST or ALT) level (> 3 × upper limit of normal [ULN], > 5×ULN, and > 10 × ULN), an elevated bilirubin level (> 1.5 × ULN and > 2 × ULN) will be presented by study visit and at any post-baseline visit. A listing of subjects who meet the laboratory criteria for Hy's law at the same visit will also be provided. The laboratory criteria for Hy's law are defined as 1) ALT or AST> 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 1.5 ULN and 2) ALT or AST> 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 2 × ULN.

13.4 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, pulse oximetry, and temperature) and weight will be summarized using descriptive statistics at baseline and at each post-baseline time point (the Day 28, 58 and 84 visit and Day 84/EOT) as well as for the most extreme result (high and low). Changes from baseline will also be summarized.

Incidence of PCS events will be presented by time point and for the most extreme post-baseline value at any visit (including unscheduled results).

Table 12.4 Vital Sign PCS Thresholds

Criteria for Treatment Emergent PCS Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20 mmHg
	Low (CL)	≤ 90	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50	Decrease of ≥ 15 mmHg
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 15 bpm
	Low (CL)	≤ 50	Decrease of ≥ 15 bpm
Temperature (°C)	Low (CL)	<36.0	NA
	High (CH)	>38.0	NA

bpm=beats per minute; C=Celsius; DBP=diastolic blood pressure; SBP=systolic blood pressure

13.5 Physical Examination

Physical examination results will be included in data listings only.

13.6 Electrocardiogram

Overall interpretation results for ECGs will be summarized using shift tables (normal, abnormal not clinically significant, and abnormal clinically significant) comparing baseline to EOT.

Descriptive statistics at baseline and at each post-baseline time point (the Day 84 visit, and Day 84/EOT), as well as changes from baseline, will be summarized for each ECG parameter (ventricular rate, RR, PR, QRS, QT, QTcF).

In addition, a categorical summary of abnormal corrected QT interval (QTc) values will be presented. At each time point, the number of subjects with QTc according to Fridericia's formula (QTcF= QT/(RR^1/3) (seconds)) and exceeding the thresholds below will be presented.

Table 12.6 ECG PCS Thresholds

ECG Parameter	PCS threshold
QTc (high), unadjusted and Fridericia's	>450 msec
	>480 msec
	>500 msec
QTc (increase), unadjusted and Fridericia's	>30 msec from baseline
	>60 msec from baseline

Source is ICH E14 ECG QTcF category thresholds.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

There are no changes from the protocol specified analyses.

15. REFERENCE

A.P. Magiorakos, A. Srinivasan2 , R. B. Carey , Y. Carmeli , M. E. Falagas5, C. G. Giske , S. Harbarth , J. F. Hindler , G. Kahlmeter , B. Olsson-Liljequist, D. L. Paterson, L. B. Rice, J. Stelling, M. J. Struelens1 , A. Vatopoulos, J. T. Weber and D. L. Monnet, Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance, Clin Microbiol Infect 2012; 18:268-281 (published online 7 May 2011).

16. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

General

- Specialized text styles, such as bold, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings (TFLs) unless they add significant value to the TFL.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters and printer- or font-specific characters, will not be used in a TFL.
- Hexadecimal character representations are allowed (e.g., μ, α, and ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and add value to the TFL.

Tables

- Means and medians will be presented to 1 decimal place more than the raw data. Standard deviations will be presented to 2 decimal places more than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data. For parameters that are a mixture of raw and calculated values (for example height which can be either recorded in or converted to centimeters), the number of decimal places will be based on the raw data.
- Percentages will be presented to the tenths place.
- Unless otherwise specified, for frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to “lost to follow-up,” this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.

- Lower and upper CI values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25% and 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source table number(s), if applicable (in case aggregated results, such as the mean or median, are plotted), source listing(s) (in case individual responses are plotted), and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".
- Line graphs over time of change from baseline results will include a horizontal dashed reference line at zero.

Listings

- If not otherwise specified, all data listings will be sorted by subject number, treatment, visit, and date/time, as appropriate.
- All date values will be presented in a SAS® statistical software, version 9.4 or higher (SAS Institute Inc) date format (e.g., 29AUG2001).
- All observed time values will be presented using a 24-hour clock format (HH:MM:SS) (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Missing or Incomplete Dates

Adverse Events and Concomitant Medications

The most conservative approach will be systematically considered. If the adverse event (AE) onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a treatment-emergent AE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant medication.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of the first dose of test article, provided the start month and year are the same as the date of the first dose of test article and stop date is either after the date of the first dose of test article or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of the first dose of test article, provided the start year is the same as the date of the first dose of test article and stop date is either after the date of the first dose of test article or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and stop date is either after the date of the first dose of test article or completely missing, then the start date will be estimated to be equal to the date of the first dose of test article. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing, and January 1 will be used if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day of resolution of the event will be assumed to be the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the day of resolution of the event will be assumed to be the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).

- If the stop date of the event is completely missing or event is continuing, the event resolution will be assumed to be after the first dose of test article, and the stop date will be imputed using the last known date on the study.

Medical History (including NTM History)

Missing day and month of the onset or end date of a medical history term (including NTM history) will not be imputed. However, if the month and year are present, the day will be imputed to 01.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days: A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the following formula: duration in days = date2 – date1 + 1
- Height: Height entries made in inches are converted to centimeters using the following formula: height (cm) = height (in) × 2.54
- Weight: Weight entries made in pounds are converted to kilograms using the following formula: weight (kg) = weight (lb)/2.2046
- Temperature: Temperature entries in degrees Fahrenheit are converted to degrees centigrade using the following formula: temperature (° C) = 5/9 × [temperature (° F) – 32]
- Body Mass Index (BMI): BMI is calculated using height and weight using and is calculated using the following formula: BMI (kg/m^2) = weight (kg) / [[height (cm) / 100]^2]
- Change from baseline: Change from baseline will be calculated using the following formula: change = post-baseline value – baseline value

APPENDIX B: SAS PROGRAMMING QUALITY CONTROL REQUIREMENTS

Derived datasets are independently programmed by 2 programmers. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study analysis dataset specifications provided to the client at study conclusion.

Tables and listings are independently reprogrammed by a second programmer.

Listings are checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.

Refer to TMP-SOP-0205-003 “QC Requirements” for further details.

APPENDIX C: TABLE, FIGURE, LISTING LAYOUTS

TLF mocks are contained in a separate document.

APPENDIX D: DMID ADULT TOXICITY TABLE

The DMID Adult Toxicity Table (21-NOV-2007) was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. Grades for enzymes were modified as indicated in the table below.

For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied.

For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL.

HEMATOLOGY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (gm/dL)	> 10.5	9.5-10.5	8.0-9.4	6.5-7.9	< 6.5
Absolute Neutrophil Count (count/mm^3)	> 1500	1000-1500	750-999	500-749	< 500
Platelets (count/mm^3)	≥ 100,000	75,000-99,999	50,000-74,999	20,000-49,999	< 20,000
WBCs (count/mm^3)	1000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	> 30,000 or < 1,000

CHEMISTRY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia (mEq/L)	> 135	130-135	123-129	116-122	< 116
Hypernatremia (mEq/L)	< 146	146-150	151-157	158-165	> 165
Hypokalemia (mEq/L)	> 3.4	3.0-3.4	2.5-2.9	2.0-2.4	< 2.0
Hyperkalemia (mEq/L)	< 5.6	5.6-6.0	6.1-6.5	6.6-7.0	> 7.0
Hypocalcemia (mg/dL) (corrected for albumin)	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	< 6.1
Hypercalcemia (mg/dL) (correct for albumin)	≤ 10.5	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
Hypomagnesemia (mEq/L)	> 1.4	1.4- 1.2	1.1-0.9	0.8-0.6	< 0.6
Hypophosphatemia (mg/dL)	≥ 2.5	2.0-2.4	1.5-1.9	1.0-1.4	< 1.0
Hyperbilirubinemia (total bilirubin)	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.5×ULN	> 2.5-5×ULN	> 5×ULN
	< 1.1×ULN	1.1-1.5×ULN	> 1.5-3.0×ULN	> 3.0-6×ULN	> 6×ULN

ENZYMES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
ALT (SGPT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
GGT	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Alkaline Phosphatase	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Lipase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN

APPENDIX E: DIRECTIONALITY OF WORST LABORATORY PARAMETERS

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Red blood cell count	Lowest value
	Mean corpuscular hemoglobin	Lowest value
	Mean corpuscular hemoglobin concentration	Lowest value
	Hemoglobin	Lowest value
	Mean corpuscular volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value

Laboratory Test	Parameter	Worst Value
	Eosinophils	Highest value
	Neutrophils	Lowest value
Chemistry		
	Alkaline phosphatase (ALP)	Highest value
	Alanine aminotransferase (ALT)	Highest value
	Aspartate aminotransferase (AST)	Highest value
	Blood urea nitrogen	Highest value
	Calcium	Both highest value and lowest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine phosphokinase (CK)	Highest value
	Gamma-glutamyl transpeptidase (GGT)	Highest value
	Lipase	Highest value
	Magnesium	Both highest value and lowest value
	Phosphorus	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
Coagulation	Prothrombin time international normalized ratio (INR)	Highest value

Ptk0796-ntm-20203 SAP_v5.0

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Agreement completed.
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