CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 15-0020
Study Title:

Targeted Reduction of Antibiotics Using Procalcitonin in a Multi-center, Randomized, Double-Blinded, Placebo-Controlled Non-Inferiority Study of Azithromycin Treatment in Outpatient Adults with Suspect Lower Respiratory Tract Infection (LRTI) and a Procalcitonin (PCT) Level of ≤0.25 ng/mL (TRAP-LRTI)

NCT03341273

Version 1.0

DATE: 28JAN2021

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 15-0020**
Development Phase:	Not Applicable, IDE exempt
Products:	Diagnostic Device: VIDAS© 3 platform and VIDAS® B.R.A.H.M.S Procalcitonin (PCT) test Study Drugs: Azithromycin and matching placebo
Form/Route:	Oral Capsule
Indication Studied:	Lower Respiratory Tract Infection (LRTI)
Sponsor:	Division of Microbiology and Infectious Diseases (DMID) National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH)
Clinical Trial Initiation Date:	December 4, 2017
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Version Number:	Version 1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

ACI	Adequate Clinical Improvement
AE	Adverse Event
ALT	Alanine Aminotransferase
ATP	According-to-Protocol
ARLG	Antibacterial Resistance Leadership Group
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases
DOOR	Desirability
DSMB	Data and Safety Monitoring Board
D5V	Day 5 Visit
D11V	Day 11 Visit
D28V	Day 28 Visit
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ED	Emergency Department
ER	Emergency Room
F	Fahrenheit
GGT	Gamma Glutamyl Transferase
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-to-Treat
L	Liter
LRS	Solicited Systemic Events and LRTI Symptom Form
LRT	Assessment of LRTI Symptoms and Fever Form

List of Abbreviations *(continued)*

LRTI	Lower Respiratory Tract Infection
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mL	Milliliter
MAR	Missing at Random
MAV	Medically Attended Visit
MCAR	Missing Completely at Random
MN	Miettinen–Nurminen
MNAR	Missing Not at Random
N	Number (typically refers to subjects)
NIH	National Institutes of Health
OCO	Ordinal Clinical Outcome
OCOs	Ordinal Clinical Outcomes
PCT	Procalcitonin
PI	Principal Investigator
PT	Preferred Term
RADAR	Response Adjusted for Days of Antibiotic Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
U	Units
UADE	Unanticipated Adverse Device Effect
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "Targeted Reduction of Antibiotics Using Procalcitonin in a Multi-center, Randomized, Double-Blinded, Placebo-Controlled Non-Inferiority Study of Azithromycin Treatment in Outpatient Adults with Suspect Lower Respiratory Tract Infection (LRTI) and a Procalcitonin (PCT) Level of ≤0.25 ng/mL (TRAP-LRTI)" (DMID Protocol 15-0020) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

This is a randomized, double-blinded, placebo-controlled, non-inferiority multicenter clinical trial of azithromycin vs. placebo in adults presenting as outpatients with suspect LRTI and a PCT level of ≤ 0.25 ng/mL, as a strategy for reducing antibiotic prescriptions. The study is designed and powered for the primary analysis of a comparison of the efficacy of azithromycin versus placebo on Day 5 (i.e., after 4 days of treatment) in subjects with suspect LRTI and PCT levels of ≤ 0.25 ng/mL at enrollment using a non-inferiority approach. Subjects with a PCT value ≤ 0.25 ng/mL are randomized 1:1 to either enter a 5 day course of oral azithromycin or matching placebo. Randomization is stratified by clinical site. Subjects with a PCT > 0.25 ng/mL remained enrolled for chart review but were not to be randomized to receive study drug.

The study follows a variety of clinical improvement criteria for the primary endpoint as described in Section 3.3.

2.1. Purpose of the Analyses

Analysis of clinical improvement will be used to assess the efficacy of Azithromycin versus placebo. Non-inferiority of placebo versus azithromycin on Day 5 will be the primary analysis. The secondary outcome measures include Clinical Improvement on Days 11 and 28, and Response Adjusted for Days of Antibiotic Risk (RADAR) analysis. All components of clinical improvement and Desirability Of Outcome Ranking (DOOR) will also be analyzed individually.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary:

1. To compare the efficacy of azithromycin versus placebo on Day 5 (i.e., after 4 days of treatment) in subjects with suspect LRTI and PCT levels of ≤0.25 ng/mL at enrollment using a non-inferiority approach.

3.1.2. Secondary:

1. To compare groups receiving azithromycin versus placebo with regard to all antibiotic use by Days 11 and 28.
2. To compare groups receiving azithromycin versus placebo with regard to return visits to a physician's office or urgent care by Days 11 and 28.
3. To compare groups receiving azithromycin versus placebo with regard to emergency department visits by Days 11 and 28.
4. To compare groups receiving azithromycin versus placebo with regard to hospitalization by Days 11 and 28 if not hospitalized at the enrollment and randomization visit.
5. To compare groups receiving azithromycin versus placebo with regard to improvement in presenting symptoms by Days 11 and 28.
6. To compare the efficacy of azithromycin versus placebo on Day 11 in subjects with suspect LRTI and PCT levels of ≤0.25 ng/mL at enrollment using a non-inferiority approach.
7. To compare the efficacy of azithromycin versus placebo on Day 28 in subjects with suspect LRTI and PCT levels of ≤0.25 ng/mL at enrollment using a non-inferiority approach.
8. To compare the efficacy of azithromycin versus placebo in subjects with suspected LRTI and PCT levels of ≤0.25 ng/mL at Day 5 using a superiority approach, employing the RADAR methodology.
9. To compare groups receiving azithromycin versus placebo in regard to solicited events by Day 5.
10. To compare groups receiving azithromycin versus placebo in regard to hospitalization or visits to an Emergency Department (ED), outpatient clinic, or urgent care center for worsening or persistent LRTI after randomization by Day 5.
11. To compare groups receiving azithromycin versus placebo in regard to improvement in vital sign abnormalities or symptoms present at enrollment, on Day 5.
12. To compare groups receiving azithromycin versus placebo in regard to new vital sign abnormalities or symptoms on Day 5, or deterioration in symptoms relative to the enrollment visit on Day 5.

3.1.3. Exploratory:

1. To compare PCT levels at Day 1 and Day 5 among treatment failures in the placebo and azithromycin groups.
2. To compare the efficacy of azithromycin versus placebo in subjects with suspected LRTI and PCT levels of ≤0.25 ng/mL at Day 11 using a superiority approach, employing the RADAR methodology.

3. To compare groups receiving azithromycin versus placebo in regard to solicited events by Day 11.
4. To compare groups receiving azithromycin versus placebo in regard to hospitalization or visits to an ED, outpatient clinic, or urgent care center for worsening or persistent LRTI after randomization by Day 11.
5. To compare groups receiving azithromycin versus placebo in regard to improvement in vital sign abnormalities or symptoms present at enrollment, on Day 11.
6. To compare groups receiving azithromycin versus placebo in regard to new symptoms on Day 11, or deterioration in symptoms relative to the enrollment visit on Day 11.

3.2. Endpoints

3.2.1. Primary Endpoints

The primary endpoint is the efficacy of azithromycin versus placebo on Day 5 will be based on clinical improvement.

3.2.2. Secondary Outcome Measures

1. All antibiotic use from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group.
2. The proportion of subjects with one or more unplanned return visits to a physician's office or urgent care for persistent or worsening LRTI from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group.
3. The proportion of subjects with one or more emergency department visits for persistent or worsening from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group.
4. The proportion of subjects with one or more hospitalizations for persistent or worsening LRTI (if not hospitalized at the enrollment visit) from Day 1 through Day 11 and from Day 1 through Day 28 in each treatment group.
5. The proportion of subjects exhibiting improvement in at least one presenting symptom at Day 11 and at Day 28 in each treatment group.
6. The efficacy of azithromycin versus placebo on Day 11 will be based on clinical improvement.
7. The efficacy of azithromycin versus placebo on Day 28 will be based on clinical improvement.
8. Outcome assessed employing a superiority analysis using the RADAR approach.
    - The endpoint/outcome measure is the composite overall DOOR at Outcome Assessment on Day 5.
9. Proportion of subjects reporting solicited adverse events from Day 1 to Day 5 in each treatment group.
10. Proportion of subjects reporting one or more hospitalization or visits to an ED, outpatient clinic, or urgent care center (after randomization) for worsening or persistent LRTI from Day 1 through Day 5 in each treatment group.
11. The proportion of subjects exhibiting improvement in at least two presenting signs or symptoms at Day 5 in each treatment group.

12. The proportion of subjects exhibiting worsening or deterioration in at least one or more symptoms at Day 5 in each treatment group. The proportion of subjects with a new occurrence of a vital sign abnormality at Day 5 in each treatment group.

3.2.3. Exploratory Outcome Measures

1. Mean change in PCT levels from Day 1 and Day 5 among subjects in the placebo and azithromycin groups and among subjects with clinical improvement and clinical failures in each treatment group.
2. RADAR analysis at Day 11 (as described for Day 5 in Section 3.2.2 except temperature will be the only vital sign assessed at Day 11).
3. Proportion of subjects reporting solicited adverse events from Day 1 to Day 11 in each treatment group.
4. Proportion of subjects reporting one or more hospitalization or visits to an ED, outpatient clinic, or urgent care center for worsening or persistent LRTI from Day 1 through Day 11 in each treatment group.
5. The proportion of subjects exhibiting improvement in at least two presenting signs or symptoms at Day 11 in each treatment group.
6. The proportion of subjects exhibiting at least one new symptom on Day 11 in each treatment group. The proportion of subjects with a deterioration of one or more symptom relative to enrollment at Day 11 in each treatment group.

3.3. Study Definitions and Derived Variables

3.3.1. Timepoints

Day 5 Visit (D5V) represents Visit 3 which can occur any time from Day 5 to Day 8.

Day 11 Visit (D11V) represents Visit 4 which can occur any time from Day 11 to Day 14.

Day 28 Visit (D28V) represents Visit 5 which can occur any time from Day 26 to Day 30.

Day 1 is defined as the date of dose 1 for subjects treated with study product. For subjects not treated with study product, Day 1 will use their randomization date. The enrollment date will be used to define Day 1 for non-randomized subjects with PCT > 0.25 ng/mL. There is no Day 0 for this study, and the day preceding Day 1 will be reported as Day -1.

Study Day is defined relative to Day 1. If a visit did not occur, then study day will be imputed as its planned study day. Moreover, if a visit occurs out of the protocol defined window, then that visit will be treated as missing and its study day imputed as the planned study day in the Intention-to-Treat (ITT) analysis. Note that planned study day is 5 for D5V, 11 for D11V, and 28 for D28V.

3.3.2. Clinical Improvement at D5V

Clinical improvement at D5V is defined as fulfillment of **all** the following criteria.

1. Improvement in at least two symptoms present at enrollment (i.e., cough, sputum production, chest pain, or difficulty breathing) *or* one symptom and at least one vital sign abnormality present at enrollment. For symptoms, at least a one-step improvement (e.g., improvement from moderate to mild cough) will be considered a clinical improvement (Table 1). For vital sign abnormalities,

normalization of the presenting abnormal vital sign will be considered a clinical improvement. Qualifying vital signs and their normal values will include the following:

- temperature (<37.8°C or 100.0°F),
- pulse (<90 bpm),
- respiratory rate (≤20 breaths per minute),

2. Absence of deterioration in any qualifying symptom (i.e., cough, sputum production, chest pain, or difficulty breathing); or new vital sign abnormality not present at enrollment. For symptoms, at least a one-step deterioration (e.g. worsening from mild to moderate cough) will be considered clinical deterioration.
3. Absence of fever in the day preceding or at the D5V (fever is defined as ≥37.8 °C or 100.0 °F, measured anywhere on the body).
4. No medically attended visit to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization (persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication). **Note**: receipt of a non-study antibiotic after study day 5 will not be regarded as satisfying this definition if it is related to a new non-respiratory process that is unrelated to the prior diagnosis of LRTI

Table 1: LRTI-Related Symptoms to Define Clinical Improvement Endpoint

	Mild	Moderate	Severe
Cough*	Occasional coughing (less than hourly)	Frequent coughing (1 or more times an hour and interferes with activity or sleep)	Almost constant coughing (never free of cough or need to cough, makes activity or sleep nearly impossible)
Sputum production*	Noticeable as a problem but does not interfere with activity	Causes a great deal of inconvenience	An almost constant problem
Chest pain	Noticeable only when coughing	Noticeable during deep breaths and when coughing	Almost constant, present even when resting, without cough
Difficulty breathing*	Noticeable during strenuous activity, such as going up a flight of stairs or walking more than a block on level ground	Noticeable during light activity, or when washing or dressing	Almost constant, present even when resting
*Modified from Breathlessness, Cough, and Sputum Scale (BCSS) [Christ-Crain, Stolz D et.al]			

3.3.3. Clinical Improvement at D11V

Clinical improvement at D11V is defined as fulfillment of **all** the following criteria:

- For subjects who qualified based on the presence of at least two symptoms, then improvement must be observed in at least two symptoms present at enrollment (i.e., cough, sputum production, chest pain, difficulty breathing, or fever). For subjects who qualified based on the presence of one symptom and at least one vital sign abnormality, improvement must be observed in the one symptom present at enrollment. For symptoms other than fever, at least a one-step improvement (e.g., improvement from moderate to mild cough) will be considered a clinical improvement.
- **Note:** fever will be objectively (≥37.8 °C or 100.0 °F, measured anywhere on the body) or subjectively reported by the subject for the day preceding or on the D11V. For Day 11, fever will be

used similar to what has been done for Day 5 outcome measure definition i.e. clinical improvement requires absence of fever in the day preceding or at the D11V.

- **Note:** vital signs were not recorded at Days 11 and 28. Therefore, the subcomponents of clinical improvement at D11V and D28V are different from the subcomponents of clinical improvement used for the primary outcome measure at D5V (i.e., subcomponents at D11V and D28V do not include any reference to vital signs measures).
- Absence of deterioration in any qualifying symptom (i.e., cough, sputum production, chest pain, difficulty breathing, or fever). For symptoms other than fever, at least a one-step deterioration (e.g. worsening from mild to moderate cough) will be considered clinical deterioration.
- No medically attended visit to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization (persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication). **Note**: receipt of a non-study antibiotic after study day 11 will not be regarded as satisfying this definition if it is related to a new non-respiratory process that is unrelated to the prior diagnosis of LRTI.

3.3.4. Clinical Improvement at D28V

Clinical improvement at D28V is defined as fulfillment of **all** the following criteria:

- Improvement in at least two symptoms present at enrollment (i.e., cough, sputum production, chest pain, difficulty breathing, or fever). For symptoms other than fever, at least a one-step improvement (e.g., improvement from moderate to mild cough) will be considered a clinical improvement.
- **Note:** fever will be objectively (≥37.8 °C or 100.0 °F, measured anywhere on the body) or subjectively reported by the subject for the day preceding or on the D28V.
- **Note:** vital signs were not recorded at Days 11 and 28. Therefore, the subcomponents of clinical improvement at D11V and D28V are different from the subcomponents of clinical improvement used for the primary outcome measure at D5V (i.e., subcomponents at D11V and D28V do not include any reference to vital signs measures).
- Absence of deterioration in any qualifying symptom (i.e., cough, sputum production, chest pain, difficulty breathing, or fever). For symptoms other than fever, at least a one-step deterioration (e.g. worsening from mild to moderate cough) will be considered clinical deterioration.
- No medically attended visit to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization (persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication).

3.3.5. Desirability Of Outcome Ranking (DOOR)

DOOR is defined as follows:

- Each subject is evaluated according to the ordinal clinical outcome (OCO) (See Table 2 below).

- DOOR is then assigned according to two rules:
  - When comparing two subjects with different ordinal clinical outcomes (OCOs), the subject with a better OCO receives a higher rank.
  - When comparing two subjects with the same OCOs, the subject with fewer days of antibiotic use receives a higher rank.

Table 2: Ordinal Clinical Outcomes Assessed at D5V

OCO	Adequate Clinical Improvement* (Assessed at Outcome Assessment Day 5)	Solicited Events** (Assessed through Outcome Assessment Day 5)
1	Yes	None
2	Yes	Mild (Grade 1)
3	Yes	Moderate (Grade 2)
4	Yes	Severe (Grade 3)
5	No adequate clinical improvement with no medically attended events	None or any grade
6	No adequate clinical improvement with ED, outpatient clinic, or urgent care center visit but no hospitalization	None or any grade
7	No adequate clinical improvement with hospitalization	None or any grade
8	Death (any cause)	--
*Clinical improvement as defined in Section 3.3.2. **Solicited events are defined in Table 7.		

Table 3: Ordinal Clinical Outcomes Assessed at D11V

OCO	Adequate Clinical Improvement* (Assessed at Outcome Assessment Day 11)	Solicited Events** (Assessed through Outcome Assessment Day 11)
1	Yes	None
2	Yes	Mild (Grade 1)
3	Yes	Moderate (Grade 2)
4	Yes	Severe (Grade 3)
5	No adequate clinical improvement with no medically attended events	None or any grade
6	No adequate clinical improvement with ED, outpatient clinic, or urgent care center visit but no hospitalization	None or any grade
7	No adequate clinical improvement with hospitalization	None or any grade
8	Death (any cause)	--
*Clinical improvement as defined in Section 3.3.2. **Solicited events are defined in Table 7.		

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a randomized, double-blinded, placebo-controlled, non-inferiority multicenter clinical trial of azithromycin vs. placebo in adults presenting as outpatients with suspect LRTI and a PCT level of ≤0.25 ng/mL, as a strategy for reducing antibiotic prescriptions. The study is designed and powered for the primary analysis of a comparison of the efficacy of azithromycin versus placebo on Day 5 (i.e., after 4 days of treatment) in subjects with suspect LRTI and PCT levels of ≤0.25 ng/mL at enrollment using a non-inferiority approach.

Subjects with suspect LRTI, will be screened for the study. Qualifying symptom duration must be ≥24 hours and ≤28 days. Individuals fulfilling inclusion criteria will be approached to provide informed consent prior to the determination of the PCT level. After consent is obtained, the individual will have blood collected for PCT and a nasopharyngeal swab obtained for etiology testing. The PCT value is expected to be available to the investigator within 2 hours of the blood draw. All other clinical evaluation including laboratory testing and radiographic testing will be performed at the discretion of the treating clinician.

Subjects with a PCT value ≤0.25 ng/mL will be randomized 1:1 to receive oral azithromycin or placebo for five days, stratified by site. Randomization will occur during the same encounter as the enrollment visit. First dose of study drug should be taken within 24 hours of randomization. If a subject qualifies for randomization but chooses not to randomize, they will not be included in the analysis for the randomized group. These subjects will be withdrawn from the study due to subject withdrawal.

Randomized subjects will have efficacy outcomes measured from the time of the first dose of study drug through approximately Day 28. Efficacy outcome measures include signs and symptoms of LRTI, vital signs (temperature, pulse, respiratory rate), antibiotic usage, and return visits to see a health care professional (i.e. a physician's office, ED visits, urgent care, and hospitalizations). In addition, subjects will have blood collected for repeat PCT sample at Day 5.

Subjects with a PCT value >0.25 will not be randomized. Providers will be notified that the patient will not be randomized and therefore, the treating provider should make treatment decisions. These subjects will have their charts reviewed through approximately 28 days after screening to assess for return visits to a physician's office, ED, urgent care, and hospitalizations. Chart review may also identify whether antimicrobials were prescribed at the enrollment visit or subsequent visits through Day 29. Clinical information obtained through routine care, as detailed in Section 8.2.1, will also be documented for these subjects. This data will be used to support future research.

Subjects will be invited to contribute blood for PAXgene RNA collection at the enrollment visit (Visit 1) for future use (see Table 5). Additional informed consent will be obtained for future use sample collection.

The primary outcome measure is the non-inferiority of placebo versus azithromycin on Day 5 and will be based on clinical improvement. The secondary outcome measures include outcomes on Days 11 and 28, and RADAR analysis. See Section 3 for additional details.

4.2. Discussion of Study Design, Including the Choice of Control Groups

The goal of this study is to demonstrate the ability of a biomarker test to identify a patient population in which antibacterial treatment provides no clear benefit. This study will provide critical information to curtail the empiric use of antibiotics in a disease area of high antibacterial use – non-pneumonia LRTI, which includes tracheitis, tracheobronchitis, acute bronchitis, acute asthma exacerbation, and acute exacerbation of chronic

obstructive pulmonary disease (AECOPD). In these cases, antibiotics are frequently prescribed without proper rationale leading to avoidable adverse events and driving antibacterial resistance. The vast majority of acute non-pneumonia LRTIs presenting in outpatient settings are suspected to be of viral etiology; however, most of these cases are still treated with antibiotics. Implementation of diagnostics, such as host biomarker-based tests, to inform antibiotic use could reduce unnecessary antibiotic prescriptions. The present study focuses on patients with low PCT levels, suggesting the absence of a bacterial infection and tests the hypothesis that antibiotics can safely be withheld in this population.

The potential risk of placebo therapy is that clinical outcomes may not be equivalent to azithromycin among patients with a low PCT value. Specifically, the percent of subjects with adequate clinical improvement and without deterioration may be lower in those who did not receive azithromycin. There is also a potential risk that treatment with azithromycin may be associated with adverse events due to antibiotic-related adverse events. The magnitude of these risks is not well established, although a number of randomized trials using a PCT cutoff of ≤0.25 ng/mL suggest that withholding antibacterials in respiratory tract infections is safe and may be associated with better outcomes [5, 6, 7, and 8]. In light of this equipoise, the risks introduced in the study are no greater than those encountered in routine clinical practice. In addition, there are potential risks associated with the use of azithromycin. As the use of azithromycin in this study is consistent with its approved use, potential risks are expected to be the same as those documented on the product label: Allergic reactions, hepatotoxicity, *Clostridium difficile*-associated diarrhea, QT prolongation, and gastrointestinal upset (e.g., nausea, vomiting, diarrhea, or abdominal pain). Other treatment-related side effects occurred rarely (< 1%).

4.3. Selection of Study Population

The study will recruit potential subjects 18 years of age or older who are suspected to have LRTI. Subjects will be enrolled and randomized until the target sample size of 420 subjects (approximately 210 per group) is randomized in the PCT ≤ 0.25 ng/mL cohort. It is expected 50% of subjects meeting other entry criteria will have a PCT level of ≤ 0.25ng/mL (based on the assumption that approximately 50% of patients with LRTI will have a PCT ≤ 0.25ng/mL). Therefore, it is anticipated up to 840 subjects will be approached and enrolled to randomize 420 in the PCT level ≤ 0.25 ng/mL cohort to either azithromycin or placebo. Potential subjects will be recruited from hospital-based outpatient settings including EDs and clinics within our study sites in North Carolina (Duke University Hospital, Durham VA Medical Center), Georgia (Emory University Hospital and Atlanta VA Medical Center), and Texas (Houston VA Medical Center).

A study clinician licensed to make medical diagnoses must confirm the subject meets Inclusion and Exclusion Criteria. No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

4.3.1. Inclusion Criteria

For a list of inclusion criteria, see the most recent version of the Protocol.

4.3.2. Exclusion Criteria

For a list of exclusion criteria, see the most recent version of the Protocol.

4.3.3. Reasons for Withdrawal

Subject Withdrawal:

Subjects may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty.

A subject may withdraw or be withdrawn from the study for any of the following reasons:

- Withdrawal of consent
- Subject lost to follow-up
- Termination of the study
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons
- Any new information becomes available that makes further participation unsafe.

Subjects who wish to withdraw from further study participation will be asked to continue to participate in follow-up visits. At the time of withdrawal, subjects will undergo an early termination visit, if they are not willing to participate in the remaining follow-up visits.

Discontinuation of Treatment:

A subject may be discontinued from treatment and continue to be followed if any of individual halting rules (see Protocol) are met.

4.4. Treatments

4.4.1. Treatments Administered

Azithromycin 500 mg or placebo (administered orally as two 250 mg capsules or two matching placebo capsules) as a single dose on Day 1, followed by Azithromycin 250 mg or placebo (administered orally as one 250 mg capsule or one matching placebo capsule) once daily for 4 days (Day 2 through Day 5).

Capsules should be maintained as dispensed and not scored, cut, crushed, or otherwise divided for ease of swallowing. The capsules will be administered with water sufficient for the subject to swallow the required number of capsules.

4.4.2. Identity of Investigational Product(s)

Azithromycin, USP is an azalide antibiotic and is derived from erythromycin. Azithromycin as the dehydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}•2H_2O$ and a molecular weight of 785.0.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Per International Council on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at each participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded on screening logs maintained by each site. Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled. Only if the PCT is confirmed to be ≤0.25 ng/mL, will the subject be randomly assigned to 1 of 2 groups (1:1 ratio) to receive either azithromycin or placebo. Subjects with a PCT >0.25 ng/mL will remain enrolled but will not be randomized to receive study drug.

Enrollment of subjects will be performed online using AdvantageEDC. Lists of randomized treatment assignments will be prepared by statisticians at The Emmes Corporation and included in Emmes' Internet Data Entry System (IDES). IDES will assign each randomized subject a treatment code from the list after the necessary data has been entered into the system. Each site will have a supply of bottles pre-labeled with treatment numbers. Once a participant is assigned a treatment number, the corresponding bottle will be distributed to the participant. An unblinded pharmacist at each site will be provided with a treatment key, which links the treatment code to the actual treatment assignment, which will be kept in a secure place. Subjects will be stratified by site.

Instructions for subject enrollment are included in the Manual of Procedures (MOP). Manual back-up randomization procedures are provided in the MOP for use in the event that the site temporarily loses access to the Internet or the online enrollment system is unavailable.

4.4.4. Blinding

This is a double-blind clinical trial with respect to treatment arm. Subjects, investigators, study personnel performing any study-related assessments following randomization, and laboratory personnel performing assays will be blinded to treatment group assignment.

The study product and placebo will be dispensed by the site Research Pharmacist. The study product will be labeled with a numerical code that ensures site investigators, site staff, and subjects remain blinded to the treatment assignment. For subjects randomized to placebo, the placebo will resemble the appearance of the active study product. All study products will be packaged with an identical appearance. The site Research Pharmacist will be blinded to the treatment assignment at the time product is dispensed but may be unblinded to an individual subject's treatment assignment, if clinically indicated as determined by the treating clinician and the study's site investigator.

4.4.5. Prior and Concomitant Therapy

Administration of any medications, therapies, or vaccines including dose and frequency, will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken within 30 days prior to signing the informed consent form. Prescription and over-the-counter drugs will be included, as well as herbals, vitamins, and supplements. Subjects will also be asked specifically about the use of non-study systemic antibiotics following enrollment and through the last study visit, but no concomitant medications other than antibiotics will be recorded after enrollment.

Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Medications that might interfere with the evaluation of the study product or may compromise subject safety should not be used during the study. Medications in this category include the prohibited medications per the Subject Exclusion Criteria. In addition, the site principal investigator or appropriate sub-investigator may identify other medications that should not be used due to a risk to subject safety.

4.4.6. Treatment Compliance

The investigator will maintain records documenting all study products (azithromycin or placebo) administered to each subject for the entire study period. Subjects will be asked to complete a memory aid and bring their study product containers to D5V. The memory aid will be used to record daily study product taken, unscheduled medical visits, concomitant medications, temperature, solicited events, and specified symptoms. The study coordinator/investigator will document any missed doses of study product and provide counseling

per study sites' routine procedures to promote compliance with study product. The information on the memory aid will be recorded on a source document, but the memory aid will not be collected from the subject. If a subject's memory aid is not available, study product compliance will be obtained by subject interview. In addition, the subject will be reminded to bring the study product container for the purpose of maintaining drug accountability. If the study product container is available, product compliance will be verified by checking that the number of remaining pills (if any) is consistent with the memory aid review. The study coordinator/investigator will record how study product compliance information was obtained including options for interview, memory aid review, and study product container verification. Empty study product bottles will be discarded in accordance with site standard operating procedures.

4.5. Study Variables

The primary variables of interest in this study are clinical improvement, the DOOR, adequate clinical improvement, deterioration of symptoms, and solicited events, as defined in Section 3.3.

As the safety profile of azithromycin is well established, and this trial is not powered to detect new, unknown safety signals, there will be no azithromycin-related Adverse Event (AE) collection or Serious Adverse Events (SAEs) reporting during this study. Solicited adverse events including abdominal pain, vomiting, diarrhea, allergic reaction, and candidiasis will be collected from enrollment through D11V. Unanticipated Adverse Device Effects (UADEs) will be collected using the SAE form from the first study enrollment through study completion regardless of their relationship to study procedures.

5. SAMPLE SIZE CONSIDERATIONS

The null hypothesis corresponding to the primary analysis if this study is:

Null hypothesis: $\pi_{placebo} - \pi_{azithromycin} \leq$ -12.5%,

Alternative hypothesis (non-inferiority): $\pi_{placebo} - \pi_{azithromycin} >$ -12.5%,

where π represents the probability of clinical improvement at study day 5. 12.5% is the non-inferiority margin used for this study.

The study was first designed assuming that 840 subjects would have to be enrolled in order to randomize 420 (50%) subjects and have 80% power to rule out a 12.5% increase in the clinical improvement rate with antibiotic therapy compared to placebo assuming a clinical improvement rate of 80% in each group using a two-sided 95% confidence interval (CI) using normal approximation with continuity correction with continuity correction, in the according-to-protocol analysis population at D5V (ATP-5) as defined in Section 6.3 (i.e., allowing for 15% loss in each treatment group).

These assumptions underlying the original target sample size of 420 subjects were assessed by a planned, interim, blinded analysis after approximately 210 subjects completed or terminated from the study. The interim report was finalized on January 9th, 2020. The observed clinical improvement rate at the time of the interim analysis was 57.6% in each group which is lower than the initially assumed 80% rate. Due to this finding, new sample size estimates have been generated to account for actual observed rates of clinical improvement and protocol deviations that preclude inclusion in the primary analysis. The total sample size was increased to enroll 674 subjects which will allow 560 subjects eligible for the ATP-5 analysis population allowing for 16.9% loss in each treatment group to follow up/rescue medication. This new sample provides 80% power to rule out a 12.5% increase in the clinical improvement rate with antibiotic therapy compared to placebo assuming a clinical improvement rate of 57.6% in each group using a two-sided 95% CI with continuity correction, in an according-to-protocol analysis (i.e., allowing for 16.9% loss in each treatment group to follow up/rescue medication).

Although analysis using an ATP population was used for determination of sample size (to account for missing data), the primary analysis will be an ITT analysis using all randomized subjects.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment arm in the following order:

- Azithromycin
- Placebo

All summary tables will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2. Timing of Analyses

Interim analysis of safety data will be conducted annually at the completion of each respiratory season. There will be no interim analysis of efficacy or futility. An interim analysis will be performed to assess the assumptions used for sample size calculations including rate of adequate clinical improvement, rate of evaluable subjects and the frequency of enrolled subjects with PCT $\leq$ 0.25 ng/mL.

The final analysis will be performed after database lock.

6.3. Analysis Populations

The primary analysis will be done using the intention-to-treat (ITT) cohort. Other analyses may use according-to-protocol (ATP) cohorts. Analyses of the ITT cohort will include imputation for missing clinical improvement and DOOR.

Reasons for exclusion from each analysis population are summarized in Table 9 and shown by subject in Listing 5. Excluded subjects might satisfy multiple criteria justifying their exclusion but will have only one reason indicated in Table 9 and Listing 5. The exclusion reason indicated will be determined by first exclusion reason met based on the following rules in the order they are listed for each analysis population.

Safety Population Exclusions:

- Subject not treated with any dose of study product

ITT Population Exclusions:

- Non-randomized subjects

ATP Population Exclusions:

- Subject was excluded from ITT
- Subject had major protocol deviation related to I/E criteria
- Did not consume 5 doses of study product by D5V
- First dose of study product not taken within 24 hours of randomization
- Dosing not resumed within 24 h of a missed dose

ATP-5 Population Exclusions:

- Subject was excluded from ATP population
- Subject did not complete D5V
- D5V occurred out of the protocol defined window of Day 5 + 3 days
- D5V was not completed in person
- Data collected is insufficient to define clinical improvement at D5V

ATP-11 Population Exclusions:

- Subject was excluded from ATP population
- Subject did not complete D11V
- D11V occurred out of the protocol defined window of Day 11 + 3 days
- Data collected is insufficient to define clinical improvement at D11V

ATP-28 Population Exclusions:

- Subject was excluded from ATP population
- Subject did not complete D28V
- D28V occurred out of the protocol defined window of Day 28 ± 2 days
- Data collected is insufficient to define clinical improvement at D28V

6.3.1. Intention-to-Treat Analysis (ITT) Population

The ITT population will include all subjects with PCT ≤ 0.25 ng/mL randomized to receive study product. The analyses on the ITT population will be performed per randomized treatment assignment. Subjects in the ITT population with missing values for clinical improvement or DOOR will be imputed using multiple imputation. Baseline variables and presence of fever at the timepoint of interest will be used in the multiple imputation model. For DOOR, daily maximum severity of solicited events and OCO will be used in the multiple imputation model.

Subjects randomized but not treated will also be analyzed in the ITT population. If fever and solicited events data are collected post-randomization for a subject that was not treated, that data will be used in the ITT analysis to assist in imputing the clinical improvement and DOOR. For subjects treated with study product, data collected post dose 1 will be used in the imputation model.

6.3.2. According-to-Protocol (ATP) Cohorts

Subjects in an ATP analysis require no major protocol deviations and consumed 5 doses of study product by D5V. Subjects who miss a scheduled dose but resume the recommended dosing schedule within 24 hours remain eligible for ATP. As an exception, subjects who missed this window by at most 3 hours will be included in this population. What constitutes a major protocol deviation was assessed on a case-by-case basis by a DMID/VTEU/ARLG committee prior to any member of the committee being unblinded to treatment assignments. No major protocol deviations contributing to exclusion from ATP were identified. Subjects in an ATP analysis will be analyzed as treated. The ATP-5 (or ATP-11/ATP-28) populations will restrict subjects to those that meet the ATP requirements and furthermore completed their D5V (or D11V or D28V) in person

within the protocol defined time window and had sufficient data to define clinical improvement at D5V (or D11V or D28V). Missingness of DOOR will not exclude subjects from these ATP populations.

6.3.3. Safety Population

The Safety analysis population will consist of all subjects with recorded receipt of any amount of study product. The analyses on the Safety analysis population will be performed per treatment actually received.

6.4. Covariates and Subgroups

Subjects will be recruited from multiple clinical sites, and randomization will be stratified by site. No subgroup analyses will be performed. Study day of D5V and treatment indicator will be included as covariates in the linear regression model for clinical improvement at D5V. Similarly, study day of D11V and study day of D28V will be included as covariates in the linear regression model for clinical improvement for D11V and D28V, respectively. Covariates to be included in the multiple imputation models are listed in Section 8.4.

6.5. Missing Data

While all efforts will be made to minimize missing data, some missing data is expected. Whenever possible, subjects terminating from the study early will be given an early termination visit during which the available components of the clinical improvement, DOOR, and their related measures can be recorded. The primary analysis of clinical improvement will use multiple imputation with linear models to impute values using available information (treatment, randomization strata variables, and available visit information), assuming a missing at random (MAR) model. A sensitivity analysis using a tipping point analysis described in Section 8.4.1 will be performed to assess the robustness of the MI model and MAR assumption made about the missing data. Secondary analyses of clinical improvement will further examine the robustness of this analysis using ATP cohorts without imputation. Analysis of DOOR will use the ITT analysis population with missing values of DOOR imputed using multiple imputation. The analysis of DOOR will be repeated using ATP analysis populations with and without imputation of missing data to test the robustness of the multiple imputation model. Details of the multiple imputation models along with pseudocode are provided in Section 8.3.

6.5.1. Clinical Improvement at D5V

Clinical improvement at D5V is defined as fulfillment of all the following 1) Improvement in at least two symptoms present at enrollment (i.e., cough, sputum production, chest pain, or difficulty breathing) *or* one symptom and at least one vital sign abnormality present at enrollment 2) Absence of deterioration in any qualifying symptom (i.e., cough, sputum production, chest pain, or difficulty breathing); or new vital sign abnormality not present at enrollment 3) Absence of fever in the day preceding or at the D5V 4) No medically attended visit to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization. Persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication. However, receipt of a non-study antibiotic after study day 5 will not be regarded as satisfying this definition if it is related to a new non-respiratory process that is unrelated to the prior diagnosis of LRTI.

Subjects will be assessed on whether they were enrolled based on at least two qualifying symptoms (cough, sputum production, chest pain, or difficulty breathing) or based on one qualifying symptom and one abnormal vital sign. Severity recorded on the LRTI Symptoms and Fever form (LRT) for Visit 1 will be used as baseline. Vital signs results recorded on the Vital Signs form (VS1) for Visit 1 and Visit 3 will be used to

derive normal or abnormal results for temperature, pulse, and respiratory rate for baseline and D5V, respectively. Symptoms severity for D5V will be obtained from the Solicited Events form (LRS) for the event date corresponding to the Visit 3 date from the Visit Documentation form (VD4). Normal values for the vital signs are:

- temperature (<37.8°C or 100.0°F),
- pulse (<90 bpm),
- respiratory rate (≤20 breaths per minute),

6.5.1.1. Improvement in Two Symptoms or One Symptom and One Vital Sign Present at Enrollment at D5V

For symptoms, clinical improvement at D5V will be defined as presence of at least one-step improvement in two qualifying symptoms present at enrollment. For subjects who qualified based on one symptom and one vital sign, normalization of the presenting abnormal vital sign and at least one-step improvement in the symptom will be considered a clinical improvement.

6.5.1.2. Absence of Deterioration in any Qualifying Symptoms or New Vital Sign Abnormality at D5V

Clinical deterioration at D5V is defined as the deterioration in any qualifying symptoms (i.e., cough, sputum production, chest pain, or difficulty breathing) or presence of a new vital abnormality not present at enrollment. For symptoms, clinical deterioration will be determined as the presence of at-least one step deterioration (worsening from mild to moderate for example) in any qualifying symptom regardless whether the symptom was present at enrollment or not. For vital signs, clinical deterioration will be determined by the presence of new vital sign abnormality that was not present at enrollment.

6.5.1.3. Absence of Fever at D5V

Absence of fever at D5V is defined as absence of fever in the day preceding or at the day of D5V. If the subject had subjective fever or a temperature of ≥100.0°F reported on the LRT form for Visit 3 (i.e. LRTTMPF ≥ 100.0°F or LRTFEVYN = Yes), then the subject will be analyzed as having fever at D5V. Similarly, if the subject had subjective fever or a temperature of ≥100.0°F as reported on the LRS form for the date of the D5V or the day before or if the temperature from the vital sign form (VS1) for Visit 3 is ≥ 100.0°F, then the subject will also be analyzed as having fever at D5V. If none of the temperature or fever information is available, then absence of fever at D5V is missing. If at least some of that temperature information is available, but none of it indicates objective or subjective fever then the subject has absence of fever at D5V.

6.5.1.4. No Medically Attended Visit or Hospitalization for Persisting or Worsening LRTI at Any Time Post Randomization at D5V

No Medically Attended Visit (MAV) to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization (persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication). Note that receipt of a non-study antibiotic after D5V study day will not be regarded as satisfying this definition if it is related to a new non-respiratory process that is unrelated to the prior diagnosis of LRTI. Medically Attended visit information will be recorded on the MAV form.

- If MAVWSCP = 'Y' and (MAVABRX = 'Y' and (MAVA1RTI = 'Y' or MAVA2RTI = 'Y' or MAVA3RTI = 'Y'))), then MAV or Hospitalization for persistent or worsening LRTI at D5V is present.
- If MAVBRX=N or (MAVABRX = 'Y' and (MAVA1RTI ^= 'Y' and MAVA2RTI ^= 'Y' and MAVA3RTI ^= 'Y')), then MAV or Hospitalization for persistent or worsening LRTI at D5V is absent.
- If a subject did not complete D5V and had no MAV submitted, then MAV or Hospitalization for persistent or worsening LRTI at D5V is missing.
- Otherwise, if a subject completed D5V but had no MAV submitted then MAV or Hospitalization for persistent or worsening LRTI at D5V is absent.

6.5.2. Clinical Improvement at D11V and D28V

Clinical improvement at D11V is defined as fulfillment of all the following 1) For subjects who qualified based on the presence of at least two symptoms, then improvement must be observed in at least two symptoms present at enrollment (i.e., cough, sputum production, chest pain, difficulty breathing, or fever). For subjects who qualified based on the presence of one symptom and at least one vital sign abnormality, improvement must be observed in the one symptom present at enrollment 2) Absence of deterioration in any qualifying symptom (i.e., cough, sputum production, chest pain, difficulty breathing, or fever); or new vital sign abnormality not present at enrollment 3) No medically attended visit to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization. Persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication. However, receipt of a non-study antibiotic after study day 11 will not be regarded as satisfying this definition for D11V if it is related to a new non-respiratory process that is unrelated to the prior diagnosis of LRTI.

Subjects will be assessed on whether they were enrolled based on at least two qualifying symptoms (cough, sputum production, chest pain, or difficulty breathing) or based on one qualifying symptom and one abnormal vital sign. Severity recorded on the LRTI Symptoms and Fever form (LRT) for Visit 1 will be used as baseline. Symptoms severity for D11V will be obtained from the solicited events form (LRS) for the event date corresponding to the date of study day 11. Symptoms severity for D28V will be obtained from LRT form for Visit 5. Vital signs were not recorded for D11V and D28V.

6.5.2.1. Improvement in Two Symptoms or One Symptom Present at Enrollment at D11V and D28V

For subjects who qualified based on two symptoms, improvement in symptoms at D11V or D28V will be defined as presence of at least one-step improvement in two qualifying symptoms present at enrollment. For subjects who qualified based on one symptom and one vital sign abnormality, clinical improvement at D11V or D28V will be defined as the presence of at least one-step improvement in the one symptom present at baseline. If the one qualifying symptom at baseline has a missing value at D11V or D28V, then improvement in symptoms at D11V or D28V is missing, respectively.

Improvement in fever at D11V or D28V is defined as changing from presence of fever at baseline to absence of fever on D11V or D28V, respectively. Fever will be present at D11V if temperature reported on the LRS form for study day 11 is ≥100.0°F or if subjective fever is recorded on the LRS form on study day 11. A subject has fever at baseline or at D28V if the subject had subjective fever or a temperature of ≥100.0°F reported on the LRT form (i.e. LRTTMPF ≥100 or LRTFEVYN = Yes) for Visit 1 or Visit 5, respectively. If

at least some of the temperature information is available at D11V or D28V, but none of it indicates objective or subjective fever, then fever is absent at D11V or D28V respectively. If none of the temperature or fever information is available at D11V or D28V, then fever is missing at D11V or D28V, respectively.

6.5.2.2. Absence of Deterioration in Any Qualifying Symptoms at D11V or D28V

Clinical deterioration at D11V or D28V is defined as the deterioration in any qualifying symptoms (i.e., cough, sputum production, chest pain, difficulty breathing, or fever). For symptoms other than fever, clinical deterioration will be determined as the presence of at-least one step deterioration (worsening from mild to moderate) in any qualifying symptom regardless whether the symptom was present at enrollment or not. If at least one of the symptoms has a missing value at D11V or D28V and none of the observed parameters deteriorated, absence of deterioration will be missing at the corresponding visit. If none of the observed symptoms deteriorated and none of them had a missing value, then there is absence of deterioration. If at least one observed symptom deteriorated at study day 11, then there is no absence of deterioration at D11V regardless of whether any parameter has a missing value. Similarly, if at least one observed symptom deteriorated at D28V, then there is no absence of deterioration at D28V regardless of whether any parameter has a missing value.

6.5.2.3. No Medically Attended Visit or Hospitalization for Persistent or Worsening LRTI at Any Time Post Randomization at D11V and D28V

No Medically Attended Visit (MAV) to an ambulatory medical facility (e.g., ED, outpatient clinic, urgent care center) or hospitalization for persistent or worsening LRTI at any time after randomization (persistent or worsening LRTI is defined as receipt of a non-study antibiotic [parenteral or oral] treatment for LRTI or its complication). Note that receipt of a non-study antibiotic after D11V study day will not be regarded as satisfying this definition if it is related to a new non-respiratory process that is unrelated to the prior diagnosis of LRTI. Medically Attended visit information will be recorded on the MAV form. No MAV or hospitalization for persistent or worsening LRTI will then be derived as follows:

- If MAVWSCP = ‘Y’ and (MAVABRX = ‘Y’ and (MAVA1RTI = ‘Y’ or MAVA2RTI = ‘Y’ or MAVA3RTI = ‘Y’))), then MAV or Hospitalization for persistent or worsening LRTI at D11V is present.
- If MAVBRX=’N’ or (MAVABRX = ‘Y’ and (MAVA1RTI ^= ‘Y’ and MAVA2RTI ^= ‘Y’ and MAVA3RTI ^= ‘Y’)), then MAV or Hospitalization for persistent or worsening LRTI at D11V is absent.
- If a subject did not complete D11V and had no MAV submitted, then MAV or Hospitalization for persistent or worsening LRTI at D11V is missing.
- Otherwise, if a subject completed D11V but had no MAV submitted then MAV or Hospitalization for persistent or worsening LRTI at D11V is absent.

Similar derivations will be used for D28V by replacing D11V by D28V.

6.5.3. Most Severe Solicited Event for DOOR

If a subject had severity grades (0 to 3) recorded for every solicited event (abdominal pain, vomiting, diarrhea, allergic reaction, and candidiasis) from Study day 1 to D5V Study day, inclusive, then the most severe solicited event at D5V, a component of DOOR, will be the maximum severity grade taken across all solicited events from Study Day 1 to D5V Study Day.

If a subject had any solicited event of severity grade 3 from Day 1 to D5V Study Day, then the most severe solicited event at D5V will be grade 3, regardless of the presence of missing data during that period. Otherwise, if the subject has missing data for the severity grade of any solicited event from Day 1 to D5V study day, then most severe solicited event at D5V will be missing.

If a subject had severity grades (0 to 3) recorded for every solicited event (abdominal pain, vomiting, diarrhea, allergic reaction, and candidiasis) from study day 1 to study day 11, inclusive, then the most severe solicited event at D11V, a component of DOOR at D11V, will be the maximum severity grade taken across all solicited events from study day 1 to study day 11.

If a subject had any solicited event of severity grade 3 from Day 1 to study day 11 study day, then the most severe solicited event at study day 11 will be grade 3, regardless of the presence of missing data during that period. Otherwise, if a subject has missing data for the severity grade of any solicited event from Day 1 to study day 11 study day, then most severe solicited event at D11V will be missing.

A similar approach as described above will be used to determine the most severe solicited event at D28V by considering all solicited events reported post dose 1.

6.5.4. Ordinal Clinical Outcome at D5V or D11V

The OCO at D5V is defined as follows:

If the subject died at any point of study participation, then OCO at D5V will be 8.

Else if the subject has missing clinical improvement at D5V then OCO at D5V will be missing.

Else if the subject did not have clinical improvement at D5V and was hospitalized then OCO at D5V will be 7.

Else if the subject did not have clinical improvement at D5V with ED, outpatient clinic, or urgent care visit but was not hospitalized then OCO at D5V will be 6.

Else if the subject did not have clinical improvement at D5V and did not have any medically attended events then OCO at D5V will be 5.

Else if the subject has missing most severe solicited event at D5V as defined in Section 6.5.3 then OCO at D5V will be missing.

Else if the subject had clinical improvement at D5V and a most severe solicited event of grade 3 at D5V then OCO at D5V will be 4.

Else if the subject had clinical improvement at D5V and a most severe solicited event of grade 2 at D5V then OCO at D5V will be 3.

Else if the subject had clinical improvement at D5V and a most severe solicited event of grade 1 at D5V then OCO at D5V will be 2.

Else if the subject had clinical improvement at D5V and did not experience any solicited event through D5V (i.e.; the most severe solicited event at D5V is of grade 0) then OCO at D5V will be 1.

The OCO at D11V is defined in a similar manner by replacing D5V by D11V in the above algorithm.

Note that in some cases OCO can be defined even if some components are missing. For instance, if a subject had record of receipt of study product and did not have clinical improvement at D5V, OCO at D5V would still be defined even if most severe solicited event at D5V was missing since the above algorithm doesn't take solicited events severity into account for OCO levels 5, 6, 7, and 8.

6.5.5. Number of Days of Antibiotic Use at D5V, D11V, or D28V

Analysis involving comparisons of the number of days of antibiotic use will consider all antibiotic use from Day 1 onwards including study antibiotics and non-study antibiotics for systemic use. The number of days of antibiotic use is defined as the actual number of days of antibiotic use (any amount of study product that is not placebo, or any amount of other systemic antibiotic) from Day 1 to D5V study day inclusive for D5V, from Day 1 to D11V study day inclusive for D11V, and from Day 1 through D28V study day inclusive for D28V. For subjects that received placebo as study product, it is counted as the number of days of systemic antibiotic as determined solely from the concomitant medication form. For subjects that receive actual antibiotic as study product, it is counted as the number of days that the subject received any amount of either study product or a non-study systemic antibiotic, as determined from the concomitant medication form. Note that missed doses of study product do not necessarily lower the number of days of antibiotic use as long as a separate dose of antibiotic (study product antibiotic or concomitant medication antibiotic) was received on that day. The number of days of antibiotic use is missing (at D5V, D11V, and D28V) if the product administration record was not completed for the subject and the subject did not have non-study systemic antibiotic use during the study period recorded as a concomitant medication.

The number of days of antibiotic use at the time of analysis will be determined from the product administration records and concomitant medication records only. Data management activities and site queries (outside the scope of this document) prior to data lock will ensure concomitant medication records are as complete as possible and consistent with other records (i.e., AEs and medically attended visit records in the clinical database). The number of days of antibiotic use for a concomitant medication will be calculated as the medication end date minus the medication start date plus one day. Days will not be double counted if multiple systemic antibiotics (including antibiotic as study product) are taken on the same day. Systemic antibiotic use will not be counted for days that fall outside of the range being considered for each subject (Days 1 to D5V study day, or Day 1 to D11V study day, or Day 1 to D28V study day).

If there is a start date but not an end date for a concomitant medication in the clinical database, then the end date for analysis will be imputed as follows. If the subject completed the study, then the end date for analysis will be reported as the protocol completion date. If the subject terminated early from the protocol and there is at least one other record for the same antibiotic in the concomitant medications records with start and end date known (record may belong to any subject), the end date of treatment for that antibiotic will be imputed by adding the mean observed number of days of treatment rounded up to the nearest integer for that antibiotic (minus 1). If no such records exist for the antibiotic and the subject terminated early, the end date of treatment for that antibiotic will be imputed by adding to the start date the mean observed number of days of treatment rounded up to the nearest integer for all systemic antibiotics in the concomitant medication records (minus 1).

6.5.6. Desirability of Outcome Ranking (DOOR) at D5V or D11V

DOOR at D5V is defined by ranking all subjects (pooling together both treatment arms) according to OCO at D5V (lower is better) and using the number of days of antibiotic use at D5V (lower is better) as a tie-breaker for comparing the ranking of two subjects with the same OCO. DOOR at D11V is defined by ranking all subjects (pooling together both treatment arms) according to OCO at D11V (lower is better) and using the number of days of antibiotic use at D11V (lower is better) as a tie-breaker for comparing the ranking of two subjects with the same OCO. DOOR at D5V or at D11V is missing only if OCO or number of days of antibiotic use is missing for the respective visit.

The ranking algorithm for DOOR is implemented as follows. A score variable is created that adds the number of days of antibiotic use (as defined in Section 6.5.5) divided by 100 to the OCO. Subjects are then ranked

(DOOR) by the score, with the highest rank going to the subject with the lowest score, and the lowest rank going to the subject with the highest score. Tied scores result in a DOOR equal to the mean of the tied ranks. The algorithm is exemplified below using a simple scenario with 4 subjects.

Suppose Subject A has an OCO of 1 and 5 days of antibiotic use in the study period (score=1.05), Subject B has an OCO of 1 and 0 days of antibiotic use (score=1.00), Subject C has an OCO of 2 and 0 days of antibiotic use (score=2.00), and Subject D has an OCO of 1 and 5 days of antibiotic use (score=1.05). Because Subject B has the lowest score, Subject B is given DOOR=1 (the highest rank). Because Subject A and Subject D tie for the next lowest score, they both receive the mean of the next 2 available ranks (2 and 3, which has mean 2.5), and so the DOOR for both Subject A and Subject D is 2.5. Finally, Subject C has the highest score and therefore receives the worst available rank, which is DOOR=4.

6.6. Interim Analyses and Data Monitoring

There will be no interim analysis of efficacy or futility. An interim analysis was performed to assess the assumptions used for sample size calculations including rate of adequate clinical improvement, rate of evaluable subjects, and the frequency of enrolled subjects with PCT ≤0.25 ng/mL.

Assumptions underlying the original target sample size of 420 subjects were assessed by a planned, interim, blinded analysis after 213 subjects completed or terminated from the study. The original assumptions were that the overall rate of clinical improvement at Visit 3 would be 80% and that there would be no more than 15% unevaluable subjects (i.e. withdraw, fail to complete D5V or didn't meet other inclusion criteria for the according-to-protocol population at Day 5). In this interim analysis, the required sample size needed for 80% power to rule out a 12.5% increase in the clinical improvement rate with antibiotic therapy compared to placebo was computed using the observed overall rate of clinical improvement across both treatment groups and the observed proportion of subjects eligible for an according-to-protocol analysis at D5V. The findings of the interim analysis concluded that 674 subjects needed to be randomized to achieve an ATP-5 sample size of 560 (280 per arm) to achieve 80% power using clinical improvement rate of 57.6% in each group allowing for 16.9% loss in each treatment group. The protocol was updated to reflect the updated sample size.

6.7. Multicenter Studies

This is a multicenter study. Data will be pooled across all clinical sites and analyses will not adjust for potential site effects. However, indicators for site of enrollment will be used in the multiple imputation models.

6.8. Multiple Comparisons/Multiplicity

Only one hypothesis test will be performed for the primary analysis. Secondary and exploratory analyses will not be corrected for multiplicity.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Reasons for screening failures will be summarized in Table 12. The completion status and reasons for early termination or treatment discontinuation will be summarized (Table 8 and Listing 2). A subject could be discontinued early due to an AE (serious or non-serious), loss to follow-up, non-compliance with study, voluntary withdrawal, withdrawal at the investigator request, termination of the site by the sponsor, termination of the study by the sponsor, death, lack of eligibility at enrollment, inadequate clinical response, or becoming ineligible after enrollment.

Subject disposition and eligibility for analysis will be summarized in a CONSORT flow diagram (Figure 1).

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 5, Table 6, and Listing 3). Non-subject specific protocol deviations will be in Listing 4. All subject-specific protocol deviations and non-subject specific protocol deviations will be presented. Major protocol deviations are selected by the PI/DMID and ARLG.

8. EFFICACY EVALUATION

All efficacy variables will be listed by subject. Data will be summarized by treatment group. Continuous efficacy variables will be summarized with the number of observations, mean, median, standard deviation, minimum, and maximum. Categorical efficacy variables will be summarized by number and percent in each category.

All statistical tests are performed at the α=0.05 significance level. The primary hypothesis is a one-sided test but uses a two-sided 95% CI to make a conclusion about non-inferiority.

8.1. Primary Efficacy Analysis

The primary efficacy analyses of clinical improvement at D5V will be performed for the ITT analysis population. Clinical Improvement at D5V is defined in Section 3.3.

8.1.1. Primary Analysis of Clinical Improvement at D5V Using ITT Population

The hypotheses corresponding to the primary analysis of this study are:

Null hypothesis: $\pi_{placebo} - \pi_{azithromycin} \leq$ -12.5%,

Alternative hypothesis(non-inferiority): $\pi_{placebo} - \pi_{azithromycin} >$ -12.5%,

where π represents the probability of clinical improvement at study D5V. 12.5% is the non-inferiority margin used for this study and is also used for all secondary non-inferiority analyses. The primary analysis alone will be used to conclude non-inferiority of placebo to azithromycin, while other analyses are supportive.

The non-inferiority of placebo versus azithromycin with respect to clinical improvement on at D5V using a non-inferiority margin of 12.5%, will be determined for the ITT analysis population using a two-sided 95% CI of the difference in proportions of clinical improvement as constructed using multiple imputation of clinical improvement with linear regression. The study day that D5V occurred on will be included as a covariate. A lower bound of the CI greater than -12.5% will result in the conclusion of non-inferiority of placebo. The imputation model will utilize available information collected at baseline and any completed study visits.

The primary analysis will use multiple imputation with a linear regression model without rounding to impute missing values of clinical improvement at D5V using the ITT population [9 and 10].

Although the linear regression without rounding can sometimes yield implausible imputed values of treatment success, Horton et.al (2003) [10] showed that this method yields an unbiased estimate of the binomial proportion.

- Let $Y_1, Y_2, \ldots, Y_N$ be independent and identically distributed (iid) Bernouilli random variables
- Let $p = E(Y_i)$ be the probability of success
- Assume that only n out of the N Bernoulli data points are observed; the rest are missing. For simplicity, assume Let $Y_1, Y_2, \ldots, Y_n$ are observed and Let $Y_{n+1}, \ldots, Y_N$ are missing. Further assume that data is Missing Completely at Random (MCAR).

For estimating p, the minimum variance unbiased estimate (MVUE) of p denoted by $\hat{p}$ which is simply the mean of observed data, i.e.,

$$\hat{p} = \frac{1}{n}\sum_{i=1}^{n} Y_i$$

Rubin and Schenker (1986) [11] proposed using a full normal imputation method to impute missing values $Y_{n+1}, \ldots, Y_N$ which assumes that the Y_i are iid from normal distribution with mean p and variance σ^2. This method follows the following algorithm to generate the missing values.

This full normal imputation method without rounding incorrectly assumes a normal distribution and can sometimes yield implausible imputed values (above 1 or below 0). However, it produces an unbiased estimate of the probability of success p.

Allison (2005) [9] showed that this approach can be extended to allow covariates in the model. Hence, using simulation studies, Allison showed that multiple imputation using linear regression performed well in estimating regression coefficients in different missing data scenarios (MCAR, MAR) even when compared to logistic regression. The added benefit of using the linear regression model is that it directly provides proportion differences along with their 95% CI after applying PROC MIANALYZE to the model fits from the M multiply imputed datasets. This approach will follow the three steps described below:

Step 1: A multiple regression model: $Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_c X_c + \epsilon_i \ , \epsilon_i \sim N(0, \sigma^2)$ where Y_i represents the indicator for clinical improvement and X_c are the covariates described in Section 8.4.1 to be used in the multiple imputation model to generate *M* multiply imputed datasets.

Step 2: A linear regression model $Y_i = \beta_0 + \beta_1 trt + \beta_2 cstday5 + \epsilon_i$ will be fit on each of the *M* multiply imputed datasets with *trt* defined as 0 for Azithromycin and 1 for Placebo and c*stday5* defined as the study day that D5V occurred on centered at the planned study day, i.e.; *cstday5=stday5-5*. The study day for D5V covariate is centered to its planned study day to facilitate interpretation of the estimates.

Step 3: The final clinical improvement estimates will be obtained by combining *M* estimates of composite cure estimates using PROC MIANALYZE as described in in Section 8.4.1. The difference in rates of clinical improvement for placebo compared to azithromycin ($p_p - p_a$) when study day of D5V is 5 will then be obtained by β_1. The rate of clinical improvement for placebo will be estimated as $p_p = \beta_0 + \beta_1$ and the rate of clinical improvement for azithromycin will be obtained by $p_a = \beta_0$ when the study day for D5V is 5. The two-sided 95% CI for the rates of clinical improvement and difference in rates in clinical improvement will use estimates from the linear regression with multiple imputation.

Rates of clinical improvement for each treatment group along with their 95% CI, a point estimate of the difference in rates of clinical improvement at D5V along with 95% CI obtained from linear regression with multiple imputation model as described above will be provided in Table 21 for D5V using the ITT analysis population.

The null hypothesis will be rejected and non-inferiority of placebo versus azithromycin with respect to clinical improvement on at D5V using a non-inferiority margin of 12.5% will be concluded if the lower bound of the 95% CI for the difference in rates of clinical improvement for azithromycin relative to placebo is greater than -12.5%. An individual listing of observed values of clinical improvement is provided in Listing 16.

8.2. Secondary Efficacy Analyses

8.2.1. Analyses of Clinical Improvement at D5V using ATP-5 Analysis Population.

The ATP-5 analysis population will have no missing values of clinical improvement, therefore the analysis of clinical improvement at D5V will be performed using a linear regression without multiple imputation with treatment group and centered study day of D5V as a covariates ($Y_i = \beta_0 + \beta_1 trt_i + \beta_2 cstday5 + \epsilon_i$) for subjects in the ATP-5 analysis population. The rate of clinical improvement in the placebo group will then be

estimated by $p_p = \beta_0 + \beta_1$ and the rate of clinical improvement in the azithromycin arm will be provided by $p_a = \beta_0$ assuming that the study day of D5V is 5.

The estimate for the difference in rates of clinical improvement given that study day of D5V is 5 will be provided by β_1 and its 95% CI will be calculated first by using the 95% CI for β_1 from the linear regression model above. As a sensitivity analysis, the 95% CI for the difference in rates of clinical improvement will be recalculated using the Miettinen–Nurminen (MN) method [13] from PROC FREQ with RISKDIFF (CL= MN) in SAS without adjusting for study day of D5V.

Rates of clinical improvement for each treatment group, a point estimate of the difference in rates of clinical improvement at D5V along with their 95% CIs obtained methods described above will be provided in Table 22 using the ATP-5 analysis population. If the lower bound of the 95% CI for the difference in rates of clinical improvement is greater than -12.5%, it will be annotated by a footnote c.

8.2.2. Analysis of Clinical Improvement at D11V and D28V Using ITT Analysis Population

Analysis of clinical improvement will be repeated for D11V and D28V using the ITT analysis population in an analogous manner as the primary analysis as described in Section 8.1.1.

The non-inferiority of placebo versus azithromycin with respect to clinical improvement on at D11V will be determined for the ITT analysis population using a 95% CI of the difference in proportions of clinical improvement as constructed using multiple imputation of clinical improvement with linear regression. The study day that D11V (or D28V) occurred on centered at the planned study day (11 for D11V and 28 for D28V) will be included as a covariate in the imputation model. The imputation model will utilize available information collected at baseline and any completed study visits as described in Section 8.4.1.

Rates of clinical improvement for each treatment group in the ITT population along with their 95% CI and a point estimate of the difference in rates of clinical improvement at D5V along with a 95% CI will be obtained using linear regression following multiple imputation and shown in Table 23 for D11V and Table 25 for D28V after adjusting for study day of D11V and D28V, respectively.

8.2.3. Analyses of Clinical Improvement at D11V and D28V Using ATP Analysis Populations

Analysis of clinical improvement will be performed for ATP-11 and ATP-28 analysis populations will be performed using the same approach used for ATP-5 described in Section 8.2.1 using linear regression model with treatment group and centered planned study day of the visit as covariates.

Rates of clinical improvement for each treatment group along with their 95% CI, a point estimate of the difference in rates of clinical improvement along with 95% CI obtained methods described in Section 8.2.1 will be provided in Table 24 for D11V using the ATP-11 analysis population and in Table 26 for D28V using the ATP-28 analysis population. If the lower bound of the 95% CI for the difference in rates of clinical improvement is greater than -12.5%, it will be annotated by asterisk symbol (*).

8.2.4. Sensitivity Analysis of Clinical Improvement, ITT Analysis Population

Robustness of the multiple imputation model for ITT analysis population will be assessed by using tipping point analysis using linear regression as described in Section 8.2.1 using linear regression adjusting for treatment group and centered study day of D5V (or D11V, D28V). A point estimate of the difference in rates of clinical improvement, placebo relative to azithromycin and its 95% CI from the linear regression model will be reported. The results of this sensitivity analyses will be provided in Table 27 for D5V, Table 28 for D11V and Table 29 for D28V.

8.2.5. Analysis of Number of Days of Antibiotics Use at D11V and D28V Using ATP Analysis Populations

Using the ATP-11 and ATP-28 analysis populations, respectively, the mean number of days of antibiotic use from Day 1 until D11V or D28V will be computed based on the definitions from Section 6.5.5 for the placebo group and the azithromycin group, in addition to an estimated difference in means for the placebo group relative to the azithromycin group using the t-test and its associated 95% CIs calculated based on t-test. The significance of the difference in means will be tested by a t-test and results from the Satterthwaite method will be provided in Table 30 and Table 31. An individual listing of days of antibiotics use is provided in Listing 16.

8.2.6. Analysis of Medically Attended Events at D11V and D28V Using ATP Analysis Populations

Proportions of subjects with one or more return visits to a physician's office or urgent care, one or more emergency department visits, or one or more hospitalizations for persistent or worsening LRTI at any time after randomization by D11V or D28V will be produced for D11V and D28V and results will be reported in Table 32, Table 33, and Table 34. Tests for differences in proportions, placebo relative to azithromycin, will be given by Fisher's Exact Test. In addition, an estimated odds ratio and its associated 95% CI calculated using the Wald Method will be provided. Listing 19 contains all medically attended visits while Listing 20 provides a listing of all hospitalizations.

8.2.7. Improvement in LRTI Symptoms at D11V and D28V Using ATP Analysis Populations

Separately for D11V and D28V, using ATP-11 and ATP-28, respectively, the proportions of subjects exhibiting improvement in at least one presenting symptom by D11V or by D28V will be computed for placebo versus azithromycin, in addition to an estimated odds ratio and its associated 95% CI. The significance of the difference in proportions will be tested by a Fisher's Exact Test. The analysis will be repeated, analyzing each symptom individually and results will be provided in Table 35 and Table 36. The Wald method will be used for calculating 95% CI for odds ratio. A listing of all LRTI symptoms is provided in Listing 17.

8.2.8. Analysis of DOOR at D5V Using ITT and ATP-5 Analysis Populations

DOOR at D5V is defined in Section 3.3.

The null hypothesis corresponding to this analysis is:

> H0: The sum of the probability that a subject assigned to placebo will have a higher DOOR at D5V Visit than if assigned to the Azithromycin plus one-half the probability of equal DOORs at D5V is 50% (i.e., no difference in DOOR at D5V).

The above null hypothesis can be tested using a Mann-Whitney U Test.

This analysis will use multiple imputation with a linear model to impute missing DOOR at D5V. Details of multiple imputation methods are described in Section 8.4.2.

For each of the 20 complete multiple imputation datasets, a Mann-Whitney U statistic will be computed using randomization to placebo versus randomization to azithromycin to define the binary grouping and DOOR at D5V as the outcome. The U statistics are asymptotically normal distributed, and so they can be combined into a single test statistic using Rubin's Rules [3].

Defining the following:

n_1: number of subjects in ITT population randomized to placebo

n_2: number of subjects in ITT population randomized to Azithromycin

m: number of imputed datasets ($m = 20$)

Q_i: U statistic computed from the i^{th} multiply imputed dataset

$\bar{Q} = \frac{1}{m}\sum_{i=1}^{m} Q_i$

Q_0: the expected value of a U statistic under the null hypothesis ($Q_0 = \frac{n_1 n_2}{2}$)

$\bar{U}$: The within imputation variance (this is not the mean of the U statistics). Correcting for ties, the formula for the within imputation variance of the Mann-Whitney U statistic is:

$$\bar{U} = \mathrm{Var}(Q_i) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \frac{1}{(n_1 + n_2)(n_1 + n_2 + 1)}\sum_{c=1}^{D}(M_c^3 - M_c)\right]$$

[2 and 4]

where M_c is the number of tied ranks for the c^{th} value DOOR in the dataset and D is the number of distinct values of DOOR in the dataset. Because the numbers of tied ranks should be very similar across the 20 multiply imputed datasets, the number of ties will be counted from the first imputed dataset only, and those counts will be used to compute the corrected variance.

$B = \frac{1}{m-1}\sum_{i=1}^{m}(Q_i - \bar{Q})^2$

$T = \bar{U} + \frac{m+1}{m}B$

$W = \frac{(\bar{Q}-Q_0)^2}{T}$

$r = \frac{m+1}{m}\frac{B}{\bar{U}}$

$\nu = (m-1)\left(1 + \frac{1}{r}\right)^2$

Under null hypothesis corresponding to the secondary DOOR analysis of this study,

$$W \sim \mathrm{F}_{1,\nu}$$

This F-distribution is used to compute a p-value (one-sided probability) from the overall test statistic W. The null hypothesis will be rejected if p<0.05.

A corresponding 95% CI for U will be computed using the overall test statistic W through the inversion of the F-test. Dividing the bounds of this CI by $n_1 n_2$ will yield the bounds for the 95% CI of Pr(Higher DOOR in placebo) + 0.5 Pr(Equal DOOR in azithromycin). Thus, the CI for DOOR probability is given by:

$$95\%\ \mathrm{CI}: \left(\frac{\bar{Q} - \sqrt{T \times F_{0.95,1,\nu}}}{n_1 n_2}, \frac{\bar{Q} + \sqrt{T \times F_{0.95,1,\nu}}}{n_1 n_2}\right)$$

A point estimate of the DOOR probability will be obtained by dividing $\bar{Q}$ by $n_1 n_2$. Results will be shown in Table 37 for ITT population.

Analysis of DOOR will be repeated for the ATP-5 analysis population and using the same multiple imputation model as ITT analysis. Results of this analysis will be reported in Table 38.

Additional analyses of DOOR at D5V will be performed using only subjects in the ATP-5 population with complete data. These analyses will test the null hypotheses described above using the Mann-Whitney U Test, estimate Pr(Higher DOOR in placebo) + 0.5 Pr(Equal DOOR) using U divided by the number of pairwise comparisons, and will compute confidence intervals by (1) inverting the Mann-Whitney U Test and (2) using a non-parametric bootstrap.

Confidence intervals from inverting the Mann-Whitney U Test will be given by:

$$\left(\frac{U}{n_1 n_2} - 1.96 \times \sqrt{\frac{\mathrm{Var}(U)}{(n_1 n_2)^2}}, \frac{U}{n_1 n_2} + 1.96 \times \sqrt{\frac{\mathrm{Var}(U)}{(n_1 n_2)^2}}\right)$$

Correcting for ties, the formula for the variance of U is:

$$\mathrm{Var}(U) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \frac{1}{(n_1 + n_2)(n_1 + n_2 + 1)} \sum_{c=1}^{D} (M_c^3 - M_c)\right]$$

where M_c is the number of tied ranks for the c^{th} value DOOR in the dataset and D is the number of distinct values of DOOR in the dataset.

Confidence intervals for the DOOR probability using a non-parametric bootstrap:

$$\left(\frac{U_{0.025}}{n_1 n_2}, \frac{U_{0.975}}{n_1 n_2}\right)$$

Where $U_{0.025}$ and $U_{0.975}$ are chosen as the 250$^{\text{th}}$ and 9750$^{\text{th}}$ values in a sorted array of 10000 values of Mann Whitney U statistics generated from random resampling (number of values sampled to generate the statistic will be equal to the number of subjects in the respective analysis population) of the empirical distributions of DOOR scores in each treatment arm for the given analysis population.

Results from the analysis using ATP-5 population with complete data will be reported in Table 48.

Summaries of OCO, a component of DOOR will also be analyzed. Number and percentage of subjects in each OCO category at D5V along with its 95% CI calculated using the Wilson method will be presented in Table 49 for the ITT analysis population, Table 50 for ATP-5 analysis population, and graphically in Figure 16. A cumulative distribution function of these OCOs at D5V will also be presented in Figure 17 for the ITT analysis population and Figure 18 for the ATP-5 analysis population. An individual listing of observed values of DOOR is provided in Listing 16.

8.2.9. Analysis of Solicited Events at D5V Using ATP-5 Analysis Population

Results of the analysis of solicited events at D5V, a component of DOOR, will be presented using forest plots of 95% CIs for the risk difference of each solicited event and the risk difference for placebo compared to azithromycin of any solicited event, for each severity threshold (mild or greater, moderate or greater, or severe) in Figure 2, Figure 3, and Figure 4. Results will also be reported in tables Table 56, Table 57, and Table 58. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests. Since Fisher's test cannot be inverted, there is no corresponding CI. Therefore, the Miettinen-Nurminen method will be used to compute all 95% CIs for risk differences. Note that the CI results might not be consistent with the p-value from Fisher's exact test.

8.2.10. Analysis of Medically Attended Events at D5V Using ATP-5 Analysis Populations

A forest plot of 95% CIs for the risk difference of one or more visits to an ED, one or more visits to an outpatient clinic, or one or more visits to an urgent care center or one or more hospitalizations for persistent or worsening LRTI at any time after randomization will be produced for D5V using ATP-5 analysis population in Figure 8 and results will also be presented in Table 43 to include a p-value from Fisher's exact test. Since Fisher's test cannot be inverted, there is no corresponding CI. Therefore, the Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences. Note that the CI results might not be consistent with the p-value from Fisher's exact test. Listing 19 contains all medically attended visits while Listing 20 provides a listing of all hospitalizations.

8.2.11. Improvement in Qualifying Symptoms or Vital Signs at D5V Using ATP-5 Analysis Population

The proportions of subjects exhibiting improvement in one qualifying symptom (cough, sputum production, chest pain, or difficulty breathing) or vital sign (temperature, pulse, respiratory rate, or pulse oximetry) at Visit 3 compared to baseline will be computed for placebo versus azithromycin along with associated 95% CIs using ATP-5 population. A forest plot of 95% CIs for the difference in proportions of subjects with improvement in any symptom or sign, any symptom, any sign, at least two symptoms or signs, and each individual symptom or sign will be provided in Figure 10. Results will also be reported in Table 41, and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. Since Fisher's test cannot be inverted, there is no corresponding CI. Therefore, the Miettinen–Nurminen method will be used to compute the 95% CIs for risk differences. Note that the CI results might not be consistent with the p-value from Fisher's exact test.

8.2.12. Deterioration in LRTI Symptoms at D5V Using ATP-5 Analysis Population

A forest plot of 95% CIs for the risk difference of deterioration in any qualifying symptom (cough, sputum production, chest pain, or difficulty breathing) at D5V compared to baseline will be analyzed in subjects having the symptom at baseline will be provided in Figure 12 using ATP-5 Analysis Population. Results will also be reported in Table 39, and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. Since Fisher's test cannot be inverted, there is no corresponding CI. Therefore, the Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences. Note that the CI results might not be consistent with the p-value from Fisher's exact test.

8.2.13. New occurrence of Vital Sign Abnormality or Fever at D5V Using ATP-5 Analysis Population

Using ATP-5, a forest plot of 95% CIs for the risk difference of new vital sign abnormality at D5V compared to baseline or fever in the 24 hours preceding or at D5V will be provided in Figure 14. Results will also be reported in Table 42 to include a p-value from Fisher's exact test. Since Fisher's test cannot be inverted, there is no corresponding CI. Therefore, the Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences. Note that the CI results might not be consistent with the p-value from Fisher's exact test.

8.3. Exploratory Efficacy Analyses

8.3.1. Analysis of PCT Levels at D5V Using ATP-5 Analysis Population

Using the ATP-5 analysis population, mean changes in PCT levels at D5V relative to baseline will be computed for placebo versus azithromycin, in addition to an estimated difference in mean PCT changes from

baseline and associated 95% CI based using bootstrap with 10000 samples. The bootstrap CI estimates will use the 2.5th and 97.5th percentiles of samples obtained by repeatedly re-sampling the empirical distribution of PCT changes from baseline with replacement for each treatment group. A similar approach will be used to estimate 95% CI for difference in mean PCT changes from baseline for placebo relative to azithromycin based. Significance of a difference in mean PCT changes for placebo compared to azithromycin will be tested by a Wilcoxon test and results will be reported in Table 62 for all subjects and separately for subjects with clinical failure and clinical improvement. As the limit of quantitation is 0.05, PCT values reported as <0.05 will be imputed as half the limit of quantitation (i.e; 0.025) for this analysis. Individual subject PCT levels are provided in Listing 12.

8.3.2. Association of Changes in PCT Levels at D5V and Clinical Improvement Using ATP-5 Analysis Population

The relationship between changes in PCT levels at D5V relative to baseline and clinical improvement at D5V will be assessed using logistic regression adjusting for treatment assignment and centered study day of D5V as covariates. Note that PCT values reported as <0.05 will be imputed as half the limit of quantitation (i.e; 0.025) for this analysis. Results will be reported in Table 63.

8.3.3. Analysis of DOOR at D11V Using ITT and ATP-11Analysis Populations

Analysis of DOOR at D11V will be performed using ITT and ATP-11 analysis populations separately and using similar methods as in Section 8.2.8. Results will be reported in Table 46 for ITT and Table 47 for ATP-11. Results from a sensitivity analysis using ATP-11 population with complete data will be reported in Table 48. Summaries of OCO, a component of DOOR will also be analyzed. Number and percentage of subjects in each OCO category at D11V along with its 95% CI calculated using the Wilson method will be presented in Table 49 for the ITT analysis population, Table 51 for ATP-11 analysis population, and graphically in Figure 16. A cumulative distribution function of these OCOs at D11V will also be presented in Figure 19 for the ITT analysis population and Figure 20 for the ATP-5 analysis population.

8.3.4. Analysis of Solicited Events at D11V Using ATP-11 Analysis Population

Results of the analysis of solicited events at D11V, a component of DOOR, will be presented using forest plots of 95% CIs for the risk difference of placebo compared to azithromycin of each solicited event and the risk difference for placebo compared to azithromycin of any solicited, for each severity threshold (mild or greater, moderate or greater, or severe) in Figure 5, Figure 6, and Figure 7. Results will also be reported in Table 59, Table 60, and Table 61, and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences.

8.3.5. Analysis of Medically Attended Events at D11V Using ATP-11 Analysis Populations

A forest plot of 95% CIs for the risk difference for placebo compared to azithromycin of one or more visits to an ED, one or more visits to an outpatient clinic, or one or more visits to an urgent care center or one or more hospitalizations for persistent or worsening LRTI at any time after randomization will be produced for D11V using ATP-11 analysis population in Figure 9 and results will also be presented in Table 44 to include a p-value from Fisher's exact test. The Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences.

8.3.6. Improvement in Qualifying Symptoms or Vital Signs at D11V Using ATP-11 Analysis Population

The proportions of subjects exhibiting improvement in any symptom, any symptom or fever, at least two symptom, and one qualifying symptom (cough, sputum production, chest pain, or difficulty breathing) or fever at D11V compared to baseline will be computed for placebo versus azithromycin along with associated 95% CIs using ATP-11 population. A forest plot of 95% CIs for the difference for placebo compared to azithromycin in proportions of subjects with improvement any symptom or fever, any symptom, each individual symptom or fever will be provided in Figure 11. Results will also be reported in Table 35, and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences for placebo compared to azithromycin.

8.3.7. Deterioration in LRTI Symptoms at D11V Using ATP-11 Analysis Population

A forest plot of 95% CIs for the risk difference for placebo compared to azithromycin of deterioration in any qualifying symptom and in each symptom individually (cough, sputum production, chest pain, or difficulty breathing) at D5V compared to baseline will be analyzed in subjects having the symptom at baseline will be provided in Figure 13 using ATP-5 Analysis Population. Results will also be reported in Table 40, and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences.

8.3.8. New occurrence of Fever at D11V Using ATP-11 Analysis Population

Using ATP-11, a forest plot of 95% CIs for the risk difference of fever in the 24 hours preceding or at D11V will be provided in Figure 15. Results of fever at D11V will also be reported in Table 45. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Miettinen–Nurminen method will be used to compute all 95% CIs for risk differences.

8.3.9. Bivariate Analysis of DOOR and Number of Days of Antibiotics Use at D5V and D11V

In addition to the DOOR analyses described in Section 8.2.8, a two-dimensional analysis of the DOOR probability and difference in the mean duration of antibiotic use in the two treatment groups will also be performed at D5V. Only subjects with non-missing DOOR and number of days on antibiotics will be included in these analyses The horizontal axis is the DOOR probability (probability of a more desirable outcome when assigned to placebo vs. azithromycin) based on the ordinal DOOR outcome ignoring the duration of antibiotic use. The vertical axis is the difference in the means of the observed (outcome not assignment) duration of antibiotic use (placebo minus azithromycin). A result in the lower right quadrant represents more desirable results for placebo, while a result in the upper left represents more desirable for azithromycin. The other two quadrants represent tradeoffs for clinical outcomes and antibiotic use.

1000 bootstrap samples will be generated by resampling with replacement from the empirical distribution of DOOR and number of days of antibiotics use at D5V. The DOOR probability and mean difference in the number of days of antibiotics use will be estimated using the bootstrap samples and plotted as a scatter plot. A 95% joint region of DOOR probability and duration for antibiotic will be constructed first using a parametric method and repeated using a nonparametric method. The parametric method will estimate the confidence region using the ellipse method from the CAR R package which uses a bivariate normal distribution. The nonparametric will use distribution-free approach implemented in the distfree.cr R package proposed by Hu and Yang (2013) in [12]. Marginal distributions of DOOR probability and difference in duration of antibiotics will be provided. To confirm the robustness of these results, these plots will be regenerated using 2000

bootstrap samples and all results will be reported in Figure 21 to include subjects in ITT population with non-missing DOOR and non-missing number of days of antibiotics use at D5V. These calculations will be repeated for D11V and results will be reported in Figure 22 to include subjects in the ITT population with non-missing DOOR and non-missing number of days of antibiotics use at D11V.

8.3.10. Longitudinal Analysis of Clinical Improvement using DOOR for ITT Analysis Population

In order to compare patterns of clinical improvement over time, multiple longitudinal analyses based on DOOR will be performed. For each of these analyses, a different definition of DOOR will be used.

8.3.10.1. Number of Times Clinical Improvement Was Achieved across D5V, D11V, and D28V

The first longitudinal analysis uses the number of days clinical improvement was achieved across D5V, D11V, and D28V to define DOOR. The number of times clinical improvement was achieved across the three timepoints for the ITT population will be calculated as:

0: No clinical improvement at any of the three timepoints

1: Clinical improvement achieved at one of the timepoints

2: Clinical improvement achieved at two of the timepoints

3: Clinical improvement achieved at all three timepoints

Missing: Clinical improvement missing for at least one of the timepoints

A summary table of frequency counts and percentages of subjects in each of the above options (0,1,2,3, Missing) across the two treatment groups will be provided in Table 52.

8.3.10.2. DOOR Analysis Based on the Number of Times Clinical Improvement Was Achieved across D5V, D11V, and D28V

To construct DOOR for this analysis, an observed number of times clinical improvement was achieved across the three timepoints will first be calculated for each subject. This calculation will be based on subjects with non-missing clinical improvement for at least one timepoint, and the observed count for each subject will ignore missingness of clinical improvement for any of the timepoints. Next, subjects will be ranked based on the observed number of times clinical improvement was achieved first without tie-breaking and repeated by using days of antibiotic use as a tie-breaker.

For the DOOR analysis without tie-breaking, subjects with a higher observed number of times clinical improvement was achieved will be assigned a higher (better) rank.

For the DOOR analysis using days of antibiotics use as a tie-breaker, subjects will be assigned DOOR according to the following two rules:

- When comparing two subjects with different observed number of times clinical improvement was achieved, the subject with a higher number of times receives a higher rank.
- When comparing two subjects with the same observed number of times clinical improvement was achieved, the subject with fewer days of antibiotic use receives a higher rank.

The null hypothesis corresponding to this analysis is:

> H0: The sum of the probability that a subject assigned to placebo will have a higher DOOR Visit than if assigned to the Azithromycin plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

The above null hypothesis can be tested using a Mann-Whitney U Test [1].

The analysis of this new DOOR will use the same approach as that described in Section 8.2.8 to estimate Prob (higher DOOR in placebo compared to Azithromycin) + ½ Prob(no difference in DOOR). The Mann Whitney test will be used to test the differences.

Results of this DOOR analysis will be reported in Table 53.

8.3.10.3. DOOR Analysis Based on the Average of Daily Ordinal Clinical Outcomes from Study Day 1 to Study Day 11

The second longitudinal analysis will use average of daily OCOs from Day 1 to Day 11 to construct DOOR.

8.3.10.3.1. Daily Ordinal Clinical Outcomes from Study Day 1 to Study Day 11

Using similar definitions for clinical improvement and most severe solicited event as those provided in Section 6.5, daily values of clinical improvement status, maximum severity of solicited symptoms, and presence of any medically attended visits will be calculated for each day. Vital signs will be excluded from the definition of daily clinical improvement since they were not collected daily. These values will then be used to calculate a daily OCO for each subject as follows:

If the subject died at any point of study participation, then OCO will be 8.

Else if the subject has missing clinical improvement at that day then OCO will be missing.

Else if the subject did not have clinical improvement at day and was hospitalized at that day then OCO will be be 7.

Else if the subject did not have clinical improvement at that day with ED, outpatient clinic, or urgent care visit but was not hospitalized that day then OCO will be 6.

Else if the subject did not have clinical improvement at that day and did not have any medically attended events for that day then OCO will be 5.

Else if the subject has missing most severe solicited event at that day as defined in Section 6.5.3 then OCO will be missing.

Else if the subject had clinical improvement at that day and a most severe solicited event of grade 3 for that day then OCO at that day will be 4.

Else if the subject had clinical improvement at that day and a most severe solicited event of grade 2 for that day then OCO will be 3.

Else if the subject had clinical improvement at that day and a most severe solicited event of grade 1 for that day then OCO will be 2.

Else if the subject had clinical improvement at that day and did not experience any solicited event for that day (i.e; the most severe solicited event for that day is of grade 0) then OCO will be 1.

Note that in some cases OCO can be defined even if some components are missing. For instance, if a subject had record of receipt of study product and did not have clinical improvement that day, OCO for that day would still be defined even if most severe solicited event was missing since the above algorithm doesn't take solicited events severity into account for OCO levels 5, 6, 7, and 8.

The daily OCOs will be presented using two graphical presentations. First a bar plot of the percentage of subjects falling in each of the daily OCO categories from study Day 1 until study Day 11 will be presented by study day and separately for each treatment group for the ITT population in Figure 23. The missing OCO category will also be added to the figure. Second, a heatmap plot of individual subject's OCO will be plotted for each day, and separate plots will be generated for the two treatment groups as presented in Figure 25. Subjects will be ordered in the heatmap figure such that subjects with the best outcome (i.e; lower values of OCO) appear at the bottom and subjects with the worst outcome or missing OCO appear at the top.

8.3.10.3.2. DOOR Analysis Daily Ordinal Clinical Outcomes from Study Day 1 to Study Day 11

To construct DOOR for this analysis, an average of observed OCO from study Day 1 to study Day 11 will be calculated for each subject ignoring missingness of data at some of the timepoints. This calculation will be based on subjects with non-missing OCO for at least one timepoint, and the average OCO calculation for each subject will ignore missingness of OCO for any of the timepoints. Next, subjects will be ranked based on their average OCO without tie-breaking.

For the DOOR analysis without tie-breaking, subjects will be ranked such that subjects with a lower average OCO are assigned a higher (better) rank while subjects with higher average OCO are assigned a lower (worse) rank.

The null hypothesis corresponding to this analysis is:

> H0: The sum of the probability that a subject assigned to placebo will have a higher DOOR Visit than if assigned to the Azithromycin plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

The above null hypothesis can be tested using a Mann-Whitney U Test [1].

The analysis of this new DOOR will use the same approach as that described in Section 8.2.8 to estimate Prob (higher DOOR in placebo compared to Azithromycin) + ½ Pob(no difference in DOOR). The Mann Whitney test will be used to test the differences.

Results of this DOOR analysis will be reported in Table 54.

8.3.10.4. DOOR Analysis Based on the Average of Ordinal Clinical Outcomes from D5V, D11V, and D28V

The second longitudinal analysis will use average of OCOs from D5V, D11V, and D28V to construct DOOR.

8.3.10.4.1. Daily Ordinal Clinical Outcomes from D5V, D11V, and D28V

Using similar definitions for clinical improvement and most severe solicited event as those provided in Section 6.5, daily values of clinical improvement status, maximum severity of solicited symptoms, and presence of any medically attended visits will be calculated D5V, D11V, and D28V as described in Section 6. Since solicited events were to be collected up to Day 11, maximum severity of solicited events post baseline will be used in deriving the most severe solicited event to be used for D28V OCO. The OCO for each

outcome for D5V and D11V will be calculated based on the algorithm in Section 6.5.4. Similarly, the OCO for D28V will be calculated by replacing D5V by D28V in the algorithm described in Section 6.5.4.

The OCOs from the above three timepoints will be presented using two graphical presentations. First a bar plot of the percentage of subjects falling in each of the OCO categories will be presented by timepoint (D5V, D11V, D28V) and separately for each treatment group for the ITT population in Figure 24. The missing OCO category will also be added to the figure. Second, a heatmap plot of individual subject's OCO will be plotted for each day, and separate plots will be generated for the two treatment groups as presented in Figure 26. Subjects will be ordered in the heatmap figure such that subjects with the best outcome (i.e. lower values of OCO) appear at the bottom and subjects with the worst outcome or missing OCO appear at the top.

8.3.10.4.2. DOOR Analysis Based on Ordinal Clinical Outcomes from D5V, D11V, and D11V

To construct DOOR for this analysis, an average of observed OCO across the three timepoints will be calculated for each subject ignoring missingness of data at some of the timepoints. This calculation will be based on subjects with non-missing OCO for at least one timepoint, and the average OCO calculation for each subject will ignore missingness of OCO for any of the timepoints. Next, subjects will be ranked based on their average OCO without tie-breaking.

For the DOOR analysis without tie-breaking, subjects will be ranked such that subjects with a lower average OCO are assigned a higher (better) rank while subjects with higher average ordinal clinical outcome are assigned a lower (worse) rank.

The null hypothesis corresponding to this analysis is:

> H0: The sum of the probability that a subject assigned to placebo will have a higher DOOR Visit than if assigned to the Azithromycin plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

The above null hypothesis can be tested using a Mann-Whitney U Test [1].

The analysis of this new DOOR will use the same approach as that described in Section 8.2.8 to estimate Prob (higher DOOR in placebo compared to Azithromycin) + ½ Prob(no difference in DOOR). The Mann Whitney test will be used to test the differences.

Results of this DOOR analysis will be reported in Table 55.

8.3.11. Association PCT Level at Screening and Detection of a Viral or Bacterial Pathogen

The relationship between PCT level at screening and detection of a viral pathogen will be assessed using logistic regression. Analysis will be repeated with detection of a bacterial pathogen as the outcome. the Results will be reported in Table 64. Individual listing of pathogens detected is provided in Listing 22.

8.4. Imputation of Missing Data

8.4.1. Multiple Imputation of Missing Values of Clinical Improvement on Day 5, Day 11, and Day 28

Primary and secondary analyses using the ITT population depend on multiple imputation of clinical improvement on D5V, D11V, and D28V. First, a table showing the number and percentage of missing data for clinical improvement on D5V, D11V, and D28V will be presented in Table 20. Regardless of the percent of missingness, multiple imputation will be used for all ITT analyses. Robustness of the multiple imputation

model will be assessed by tipping point analyses. The results of this sensitivity analyses will be provided in Table 27 for D5V, Table 28 for D11V and Table 29 for D28V. In order to use the MI model to adjust for bias caused by missing data, we assume that data is missing at random (MAR).

For missing clinical improvement on D5V, D11V, or D28V, multiple imputations of missing clinical improvement on D5V, D11V, or D28V will be performed independently, and each subject will have their missing clinical improvement imputed independently of other subjects' imputations using a subject-specific imputation model. The pseudocode shown below details how missing data for clinical improvement for D5V (D11V or D28V) will be imputed using *m* multiply imputed datasets from linear models. The following covariates will be used non-missing for the MI model: treatment group, site indicators, age, gender, study day of D5V (centered at 5), presence of fever on Day 1, and presence of fever on D5V. The number of imputed, *m*, datasets will be chosen based on the average percent of missing data. Default value will be *m*=20 since sample size calculation assumed close to 20% drop-out rate.

As a first step to multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for clinical improvement is below:

- Treatment Group (azithromycin is reference)
- Indicator of subject enrolled at the site with the second most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the third most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the fourth most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the least number of subjects enrolled (binary indicator)
    - Note: the site with the most number of subjects enrolled is reference for site. Language is written to allow for an arbitrary number of sites. In the event of a number of ties for the number of subjects enrolled, tied sites will be ordered in ascending alphanumeric order in the list of model variables.
- Age at enrollment
- Gender (Male is the reference)
- Study day of D5V (centered at 5)
- Presence of fever on Day 1 as recorded on the Assessment of LRTI Symptoms and Fever (LRT) form
- Presence of fever in the day preceding or at the D5V as recorded on Solicited Events or vital signs form

The actual list of MI model variables for each subject-specific imputation model will follow the ordering above but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification given in the pseudo-code and subjects must be processed in the order described in the pseudo-code. The pseudo-code is for D5V, but the general logic is also applicable to D11V and D28V.

```
*****************************************************************
```

*Outcome variables: clinimprove_D5V

DEFINE i=index variable for subjects having clinical improvement imputed.

Subjects requiring imputation are sorted in ascending order by PATID.

DEFINE N=number of subjects requiring imputation

DEFINE g&i=analysis dataset containing predictors and clinical improvement for

ATP-5 subjects as well as subject i (only one subject not in ATP-5 included). Note that ATP-5 subjects that are missing a value for one or more variables in the subject-specific imputation model are excluded.

DEFINE imp_g&i = g&i, with 20 imputed values for the missing clinical improvement

added by PROC MI

DEFINE &&modelVars_&i = list of observed variables in subject i (treatment group, site1, site2, site3, site4, age, gender, cstday5, fever), to be used for imputation of clinical improvement

Step 1: Imputation model: This model will generate 20 datasets with each dataset containing original complete data along with imputed values for subjects with missing endpoint.

```
%do i=1 %to &N;

PROC MI data= g&i out= imp_g&i seed= 22131&i NIMPUTE=20 noprint;
     Var &&modelVars_&i clinimprove_D5V;
     monotone regression(clinimprove_D5V) = &&modelVars_&i;
run;
%end;
```

imp_g&i will be subset to contain only rows for the subjects with imputed clinical improvement and merged together and with ATP-5 data to create the twenty complete multiply imputed datasets

Step 2: Analysis model: This model will fit regression models to the 20 complete datasets to obtain parameter estimates for treatment success, clinical cure, microbiological success.

```
proc reg data= imp_g  outest= out_clinimp_D5V covout noprint;

model clinimprove_D5V= trt cstday5/clb alpha=0.05;

by _imputation_;

run;
```

Step 3: Combine estimates from models in step 2 to obtain overall estimates summarized over 20 imputed datasets;

```
proc mianalyze data= out_clinimp
_D5 alpha = 0.05;

modeleffects intercept trt cstday5;

ods output ParameterEstimates=parms_trts;

run;

*****************************************************************
```

8.4.2. Multiple Imputation of Missing DOOR at D5V and D11V

Several analyses depend on multiple imputation of DOOR at D5V or D11V for ITT and ATP analysis populations if a significant number of data are missing. First, a table showing the number and percentage of missing data for DOOR on D5V and D11V will be presented in Table 20. In order to use the multiple imputation model to adjust for bias caused by missing data, we assume that data is missing at random (MAR).

Multiple imputations of each of these missing endpoints will be performed independently, and each subject will have their missing endpoints imputed independently of other subject's imputations using a subject-specific imputation model.

As a first step to multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for DOOR at D5V and OCO at D5V is below.

- Indicator of azithromycin as study treatment (binary indicator)
  - Note: azithromycin is the reference group for study treatment
- Indicator of subject enrolled at the site with the second most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the third most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the fourth most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the least number of subjects enrolled (binary indicator)
  - Note: the site with the most number of subjects enrolled is reference for site. Language is written to allow for an arbitrary number of sites. In the event of a number of ties for the number of subjects enrolled, tied sites will be ordered in ascending alphanumeric order in the list of model variables.
- OCO at D5V (imputed OCOs will not be used)
- Observed clinical improvement at D5V
- Study day of D5V (centered at 5)
- Presence of fever on Day 1 as recorded on the Assessment of LRTI Symptoms and Fever (LRT) form
- Presence of fever in the day preceding or at the D5V as recorded on Solicited Events or vital signs form
- Severity of most severe solicited event on Day 1 (0, 1, 2, or 3)
- Severity of most severe solicited event on Day 2 (0, 1, 2, or 3)
- Severity of most severe solicited event on Day 3 (0, 1, 2, or 3)
- Severity of most severe solicited event on Day 4 (0, 1, 2, or 3)
- Severity of most severe solicited event on D5V study day (0, 1, 2, or 3)

- Note: The D5V window is Day 1 through Day 8. Therefore, all days from Day 1 through the actual study day of D5V will be listed.

For DOOR and OCO at D11V, the complete list of model variables is identical to the above. Additionally, most severe solicited events are listed up to study day 11 rather than D5V study day and presence of fever in the day preceding or at D11V is used instead of D5V.

The actual list of model variables for each subject-specific imputation model will follow the ordering above but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification given in the pseudo-code and subjects must be processed in the order described in the pseudo-code. OCO will simultaneously be imputed with DOOR at each respective Outcome Assessment Day. The pseudo-code is in terms of D5V endpoints, but the general logic is also applicable to the D11V endpoints (with references to "D5" replaced with references to "D11").

```
DEFINE i=index variable for subjects having DOOR imputed.
      Subjects requiring imputation are sorted in ascending order
      by PATID.
DEFINE N=number of subjects requiring imputation
DEFINE g&i=analysis dataset containing predictors and DOOR for
       CC-D5 subjects as well as subject i (only one subject not in
       CC-D5 included).  Note that CC-V1 subjects that are missing a value
       for one or more variables in the subject-specific imputation model are
       excluded.
DEFINE imp_g&i = g&i, with 20 imputed values for the missing DOOR
      added by PROC MI
DEFINE &&modelVars_&i  = list of observed variables in subject i, to
      be used for imputation of DOOR and OCO.
%do i=1 %to &N;
PROC MI data=g&i out=imp_g&i seed=1200&i NIMPUTE=20 noprint;
      var &&modelVars_&i DOOR OCO;
      monotone reg(DOOR_D5V = &&modelVars_&i);
      monotone reg(OCO_D5V = &&modelVars_&i);
run;
%end;


imp_g&i will be subset to contain only rows for the subjects with imputed DOOR
and merged together and with CC-D5 data to create the twenty complete multiply
imputed datasets
```

9. SAFETY EVALUATION

Subjects in safety analyses will be analyzed according to randomization assignment, using the safety analysis population.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, gender, ethnicity, race will be presented for the PCT ≤ 0.25 ng/mL cohort by site (Table 13 and Table 15) and by treatment group and overall (Table 17 and Table 18). Similar tables will be presented for the PCT > 0.25 ng/mL cohort by site in Table 14 and Table 16. Age will be summarized as a continuous variable. Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate the subject as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option. For subjects that were previously enrolled in this study, only information associated with their second enrollment will be reported and used for analysis.

Individual subject listings will be presented for all demographics and baseline characteristics (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

Summaries of subject's medical history will be presented by MedDRA® system organ class (SOC) and treatment group (Table 19).

Physical assessment findings from the enrollment visit, and any follow up visits, will be included in Listing 7.

9.1.2. Prior and Concomitant Medications

All concomitant medications taken within 30 days of signing the informed consent or during the study period will be recorded. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. A by-subject listing of concomitant medication use will be presented (Listing 15). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group (Table 73).

9.2. Measurements of Treatment Compliance

Subjects were administered a PCT test to measure their PCT levels. Only subjects with PCT levels PCT ≤ 0.25 ng/mL were randomized to receive azithromycin or placebo. The number of subjects will be tabulated by site, treatment group, and time period of PCT screening (Table 10). Subjects were to take a single dose of the study product within 24 hours of randomization and once daily for four days. Review of the memory aid, checking of the study product container, and interview with the subject will be utilized to check treatment compliance. The number of doses of study product administered will be presented by treatment group (Table 11 and Listing 8). A listing of all subjects who took at least one dose of study product is provided in Listing 1.

9.3. Adverse Events

When calculating the incidence of AEs over multiple days (i.e., on a per subject basis), each subject will only be counted once and any repetitions of AEs within a subject will be ignored; the denominator will be the total population size on the first day of the time period (Day 1). For tabulation of AEs by day, the denominator will be the number of subjects enrolled and not withdrawn from the study by the day being described. All AEs reported will be included in the summaries and analyses.

9.3.1. Solicited Events and Symptoms

Solicited events will be captured from Day 1 until Day 11. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Solicited events were recorded for trial Days 1-11, or until study completion or termination, as the maximum severity for each day. Target solicited events include abdominal pain, vomiting, diarrhea, allergic reaction, and candidiasis.

The proportion of subjects in each treatment group experiencing each solicited event will be tabulated by treatment group (Table 65). The proportion of subjects in each treatment group experiencing each solicited event will be tabulated by treatment group and severity (Table 66). The proportion of subjects in each treatment group experiencing each solicited event will also be tabulated by day and severity level (Table 67 and Table 69). Finally, solicited events will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (mild or greater, moderate or greater, severe) (Table 68). Proportions for these derived binary variables will be reported along with 95% Cis using the Wilson method. Comparisons of proportions by treatment groups will be given as risk differences (with 95% CIs from the Miettinen–Nurminen method) and p-values from Fisher's Exact Test.

The maximum severity occurrence of each solicited event (proportion of subjects for each severity level) will be plotted for each solicited adverse event (Figure 27). Solicited events by subject will also be presented (Listing 9).

9.3.2. Unanticipated Adverse Device Effects

Any UADEs will be collected from the first study enrollment through study completion. When calculating the incidence of UADEs (i.e., on a per subject basis), each subject will only be counted once at the highest severity and/or relationship, and any repetitions of UADEs within a subject will be ignored; the denominator will be the total number of subjects in the safety population. All UADEs reported will be included in the summaries and analyses in Table 70.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

A listing of unanticipated adverse device effects will be provided in . A listing of all deaths is also provided in .

9.5. Clinical Laboratory Evaluations

No safety labs were collected for this study. Screening laboratory results are provided in Listing 10 for Chemistry and Listing 11 for Hematology. A listing of culture results is provided in Listing 21.

9.6. Vital Signs and Physical Evaluations

Vital signs will be taken at the enrollment visit and visit 3 (Day 3+1). For each visit, by treatment group, the mean, median, standard deviation, min, and max of vital sign will be calculated for temperature, pulse, respiration rate, and pulse oximetry (Table 72). Individual vital signs measurements will be listed (Listing 13) and physical exam findings will be listed (Listing 14).

9.7. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the

CRFs. A by-subject listing of concomitant medication use will be presented. The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the Safety population (Table 73).

10. OTHER ANALYSES

No other analyses are planned.

11. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as "> 0.999". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values <1% will be presented as "<1" and values >99% but below 100% will be presented as ">99". Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

12. TECHNICAL DETAILS

SAS version 9.4 or above or R version 3.2 or above will be used to perform analyses and to generate all tables, figures and listings.

13. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

In order to assess the difference in clinical improvement over time, several additional exploratory endpoints were added as described below:

- DOOR analysis based on the number of times clinical improvement was achieved across the three timepoints of D5V, D11V, and D28V.
- DOOR analysis based on the average of daily ordinal outcomes from study Day 1 to Study Day 11
- DOOR analysis based on the average of OCOs from D5V, D11V, and D28V

Additionally, a bivariate analysis of DOOR and number of days of antibiotics use at D5V and D11V will be performed.

14. REFERENCES

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15. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.5.1 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 4: Schedule of Events

	Visit #1 Screening, Enrollment, & Randomization	Visit #2*	Visit #3	Visit #4*	Visit #5*	Early Termination Visits	Visit 5N (non-randomized Subjects)
Visit Number	01	02	03	04	05		5N [8]
Visit Day[1]	Day 1	Day 3 +1	Day 5 +3	Day 11 +3	Day 28 ±2		Day 28+7
Obtain Informed Consent	X						
Assessment of Sociodemographic Data	X						
Randomization[2]	X						
Dispense study drug[3]	X						
Collection of study product bottle			X			X[7]	
Review inclusion/exclusion criteria	X						
Assessment of medication compliance		X	X			X[7]	
Assessment of Solicited AEs		X	X	X		X	
Assessment of UADEs		X	X	X	X	X	
Medical history[4]	X		X	X	X	X	X[8]
Physical exam[5]	X		X			X[7]	
Vital signs[6]	X		X			X[7]	
Assessment of LRTI signs and symptoms	X	X	X	X	X	X	
Concomitant medications[9]	X	X	X	X	X	X	X[8]
Distribute Memory Aid and Study-Related Materials	X						
Review Memory Aid		X	X	X		X[7]	
Serum or Plasma PCT	X		X			X[7]	
Nasopharyngeal Swab	X						
PAXgene Blood RNA (for future use, if consented)	X						

* Phone call assessment.
1 There will be a window around each of the scheduled follow-up assessments to allow for subject and staff flexibility.
2.Subjects with a PCT ≤0.25 ng/mL who satisfy the inclusion criteria with no exclusion criteria will be enrolled and randomized.
3. Study drug will be azithromycin or placebo.
4. Medical history will include: drug allergies, co-morbidities.
5. Physical exam will include: assessment of general appearance, a focused HEENT, neck, cardiopulmonary, and abdominal examination
6. Vital signs: temperature, pulse, blood pressure, respiratory rate, and pulse oximetry will be recorded. Care related exam findings and vital signs may be used.
7. These will be performed if indicated as part of the next regularly scheduled visit.
8. All data will be collected from a medical record review only. The subject will not be contacted.
9. All concomitant medications will be documented at Visit #1. Only non-study systemic antibiotic use will be documented at subsequent visits.

10.2 Protocol Deviations

Table 5: Distribution of Protocol Deviations by Category, Type, and Treatment Group - ITT Population

Category	Deviation Type	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Treatment administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Missed treatment administration						
	Delayed treatment administration						
	Other						
Follow-up visit schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Other						
Protocol procedure/assessment	Any type						
	Incorrect version of ICF signed						
	Blood not collected						
	Other specimen not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Specimen temperature excursion						
	Other						
Treatment administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						

Table 5: Distribution of Protocol Deviations by Category, Type, and Treatment Group - ITT Population (Continued)

Category	Deviation Type	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Blinding policy/procedure	Any type						
	Treatment unblinded						
	Other						
N= Number of subjects enrolled in the ITT Population.							

Table with similar format:

Table 6: Distribution of Protocol Deviations by Category, Type, and Treatment Group - PCT > 0.25 ng/mL Cohort

12.2.2 Displays of Adverse Events

Table 7: Solicited Adverse Event Grading Scale

	Mild	Moderate	Severe
Abdominal pain	Mild or intermittent and does not interfere with daily activity	Moderate or persistent and interferes with daily activity but did not necessitate a medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Vomiting	1 episode/day	2-3 episodes/day	≥4 episodes/day
Diarrhea	Looser than normal stools occurring 3-6 times/day	Looser than normal stools >6 times/day	Bloody diarrhea or diarrhea that requires clinical evaluation, laboratory testing, or hospitalization
Allergic reaction	New localized rash or itching without rash	New diffuse rash covering multiple areas of the body	New rash requiring clinical visit
Candidiasis	Mild mucocutaneous candidiasis, with no treatment	Moderate mucocutaneous candidiasis, requiring topical or other over-the-counter treatment	Severe mucocutaneous candidiasis; requires urgent clinical evaluation, intravenous treatment, or hospitalization

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 8: Subject Disposition by Treatment Group

PCT Level	Subject Disposition	Azithromycin		Placebo		All Subjects	
		n	%	n	%	n	%
PCT ≤ 0.25 ng/mL	Screened	--	--	--	--	x	--
	Enrolled	x	100	x	100	x	100
	Randomized	x	100	x	100	x	100
	Received Treatment	x	xx	x	xx	x	xx
	Received All Scheduled Treatments[a]	x	xx	x	xx	x	xx
	Completed D5V	x	xx	x	xx	x	xx
	Completed D11V	x	xx	x	xx	x	xx
	Completed Follow-up (D28V)[a]	x	xx	x	xx	x	xx
	Completed Per Protocol[b]	x	xx	x	xx	x	xx
PCT > 0.25 ng/mL	Screened	--	--	--	--	x	--
	Enrolled	--	--	--	--	x	xx
	Completed D28V Chart Review	--	--	--	--	x	xx

n = Number of subjects enrolled in the corresponding PCT Level and meeting the disposition criteria. Only subjects in the PCT ≤ 0.25 ng/mL were randomized to receive study product.
[a]Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.
[b]Refer to Listing 16.2.3 for reasons subjects are excluded from the Analysis populations. A subject will be counted as completed per protocol if the subject completed D28V within the protocol defined window of Day 28 ± 2 days.

Table 9: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Safety	Any Reason						
	Subject not treated with any dose of study product						
ITT	Any Reason						
	Subject not randomized						
ATP	Any Reason						
	Subject was excluded from ITT analysis population						
	Subject had major protocol deviation related to I/E criteria						
	-Deviation Type 1						
	-Deviation Type 2						
	Did not consume 5 doses of study product by D5V						
	First dose of study product not taken within 24 hours of randomization						
	Dosing not resumed within 24 h of a missed dose						
ATP-5	Any Reason						
	Subject was excluded from ATP analysis population						
	Subject did not complete D5V						
	D5V occurred out of the protocol defined window of Day 5 + 3 days						
	D5V was not completed in person						
	Data collected is insufficient to define clinical improvement at D5V						
ATP-11	Any Reason						
	Subject was excluded from ATP analysis population						
	Subject did not complete D11V						
	D11V occurred out of the protocol defined window of Day 11 + 3 days						
	Data collected is insufficient to define clinical improvement at D11V						
ATP-28	Any Reason						
	Subject was excluded from ATP analysis population						
	Subject did not complete D28V						
	D28V occurred out of the protocol defined window of Day 28 ± 2 days						
	Data collected is insufficient to define clinical improvement at D28V						

N = Number of subjects enrolled in the PCT ≤ 0.25 ng/mL cohort.

Table 10: Dates of PCT Screening by Site and Treatment Group - ITT Population

Site	Treatment Group	December 2017 - November 2018	December 2018 - November 2019	December 2019 – March 2020
Any	Any	x	x	x
Any Site	Azithromycin	x	x	x
	Placebo	x	x	x
Atlanta VA Medical Center	Azithromycin	x	x	x
	Placebo	x	x	x
Duke University	Azithromycin	x	x	x
	Placebo	x	x	x
Duke Regional Hospital	Azithromycin	x	x	x
	Placebo	x	x	x
Durham VA Medical Center	Azithromycin	x	x	x
	Placebo	x	x	x
Hope Clinic of the Emory Vaccine Center	Azithromycin	x	x	x
	Placebo	x	x	x
Houston VA Medical Center	Azithromycin	x	x	x
	Placebo	x	x	x

Table 11: Treatment Compliance by Treatment Group - ITT Population

[Implementation Note: Subjects who did not submit a product administration record (PAR) form, but who noted discontinuing from the study/treatment due to 'enrolled but treatment not administered' will be counted as having 0 doses. For subjects who did not submit a PAR form discontinued due to other reasons, they will be counted as having unknown number of doses.]

Treatment Compliance	Number of Doses Received	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		x	x.x	x	x.x	**n**	**%**
Received all scheduled doses	5 Doses	x	x.x	x	x.x	x	x.x
Received <5 doses	4 Doses	x	x.x	x	x.x	x	x.x
	3 Doses	x	x.x	x	x.x	x	x.x
	2 Doses	x	x.x	x	x.x	x	x.x
	1 Dose	x	x.x	x	x.x	x	x.x
	0 Doses	x	x.x	x	x.x	x	x.x
Treatment administration record not available	Unknown	x	x.x	x	x.x	x	xx
N=Number of subjects in the ITT Population.							

Table 12: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion/Exclusion/Eligible but Not Enrolled	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but Not Enrolled	Any Reason	x	xx
	[Reason 1]	x	xx
	[Reason 2]	x	xx

[a]More than one criterion may be marked per subject.
[b]Denominator for percentages is the total number of subjects not enrolled in this study which include screen failures and subjects eligible but not enrolled.

14.1.2 Demographic Data

Table 13: Summary of Categorical Demographic and Baseline Characteristics by Site - ITT Population

Variable	Characteristic	Atlanta VA Medical Center (N=X)		Hope Clinic of the Emory Vaccine Center (N=X)		Houston VA Medical Center (N=X)		Duke Regional Hospital (N=X)		Duke University (N=X)		Durham VA Medical Center (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Female	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Unknown	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Asian	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Native Hawaiian or Other Pacific Islander	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Black or African American	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	White	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Multi-Racial	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Unknown	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the ITT Population.

Table with similar format:

Table 14: Summary of Categorical Demographic and Baseline Characteristics by Site - PCT > 0.25 ng/mL Cohort

[Implementation note: Update the footnote to use 'Number of all subjects enrolled into the PCT > 0.25 ng/mL Cohort'.]

Table 15: Summary of Continuous Demographic and Baseline Characteristics by Site - ITT Population

Variable	Statistic	Atlanta VA Medical Center (N=X)	Hope Clinic of the Emory Vaccine Center (N=X)	Houston VA Medical Center (N=X)	Duke Regional Hospital (N=X)	Duke University (N=X)	Durham VA Medical Center (N=X)	All Subjects (N=X)
Age	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x	x	x	x	x	x	x
	Minimum	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x
N = Number of subjects in the ITT Population.								

Table with similar format:

Table 16: Summary of Continuous Demographic and Baseline Characteristics by Site - PCT > 0.25 ng/mL Cohort

[Implementation note: Update the footnote to use 'Number of all subjects enrolled into the PCT > 0.25 ng/mL Cohort']

Table 17: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group - ITT Analysis Population

Demographic Category	Characteristic	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x
	Female	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x

N = Number of subjects in the ITT population.

Table 18: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - ITT Analysis Population

Variable	Statistic	Azithromycin (N=X)	Placebo (N=X)	All Subjects (N=X)
Age	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
N = Number of subjects in the ITT population.				

14.1.3 Prior and Concurrent Medical Conditions

Table 19: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group - ITT Analysis Population

MedDRA System Organ Class	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						

N = Number of subjects in the ITT population.
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy Data

Table 20: Percentage of Subjects with Missing Data by Study Endpoint, Timepoint, and Treatment Group - ITT Analysis Population

	Azithromycin (N=X)		Placebo		All Subjects (N=X)	
Endpoint	**n**	**%**	**n**	**%**	**n**	**%**
D5V						
Clinical Improvement						
DOOR						
D11V						
Clinical Improvement						
DOOR						
D28V						
Clinical Improvement						

N = Number of subjects in the ITT population in the respective treatment group; n = Number of subjects with missing data.

Table 21: Primary Analysis of Clinical Improvement on D5V - ITT Analysis Population

Analysis Population	Statistic	Azithromycin (N=X)	Placebo (N=X)
ITT	Subjects with non-missing clinical improvement on D5V– n (%)	x (x)	x (x)
	Subjects with one or more components of clinical improvement imputed on D5V– n (%)	x (x)	x (x)
	Percent rate of clinical improvement at D5V (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
	Difference in rates (percent) of clinical improvement, placebo relative to azithromycin (95% CI)[a]	-	xx (xx, xx)
	Conclusion of non-inferiority of placebo to azithromycin[b]	-	Yes/No

N = Number of subjects in the ITT Population. Multiple imputation was used for missing values.
[a]95% CIs were obtained from linear regression model following multiple imputation adjusting for study day of D5V. The rates and difference in rates of clinical improvement presented assume that study day of D5V is 5.
[b]Non-inferiority of placebo was concluded if the lower bound of the 95% CI for the difference in proportions is greater than -12.5%.

Table 22: Analysis of Clinical Improvement on D5V - ATP-5 Analysis Population

[Implementation note: If the lower bound of 95% CI for the difference in rates of clinical improvement is greater than -12.5, annotate the interval with footnote c that states 'Lower bound of confidence interval greater than -12.5% (non-inferiority margin).']

Analysis Population	Treatment Group	Rate of Clinical Improvement			Difference in Rates		
		n	%	95% CI[a]	%	95% CI[a]	95% CI Miettinen–Nurminen[b]
ATP-5	Azithromycin (N=X)	x	xx	xx, xx	Reference	-	-
	Placebo (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx

N = Number of subjects in the ATP-5 analysis population. n = Number of subjects in ATP-5 population with clinical improvement at D5V.
[a]95% CI obtained from linear regression adjusting for study day of D5V. The rates and difference in rates of clinical improvement presented assume that study day of D5V is 5.
[b]The CI from Miettinen–Nurminen did not adjust for study day of D5V.

Table 23: Analysis of Clinical Improvement on D11V - ITT Analysis Population

Analysis Population	Statistic	Azithromycin (N=X)	Placebo (N=X)
ITT	Subjects with non-missing clinical improvement on D11V – n (%)	x (x)	x (x)
	Subjects with one or more components of clinical improvement imputed on D11V – n (%)	x (x)	x (x)
	Percent rate of clinical improvement on D11V (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
	Difference in rates (percent) of clinical improvement, placebo relative to azithromycin (95% CI)[a]	-	xx (xx, xx)
	Conclusion of non-inferiority of placebo to azithromycin[b]	-	Yes/No

N = Number of subjects in the ITT Population. Multiple imputation was used for missing values.
[a]95% CIs were obtained from linear regression model following multiple imputation adjusting for study day of D11V. The rates and difference in rates of clinical improvement presented assume that study day of D11V is 11.
[b]Non-inferiority of placebo was concluded if the lower bound of the CI for the difference in proportions is greater than -12.5%.

Table 24: Analysis of Clinical Improvement on D11V - ATP-11 Analysis Population

[Implementation note: If the lower bound of 95% CI for the difference in rates of clinical improvement is greater than -12.5, annotate the interval with footnote c that states 'Lower bound of confidence interval greater than -12.5% (non-inferiority margin).']

Analysis Population	Treatment Group	Rate of Clinical Improvement			Difference in Rates		
		n	%	95% CI[a]	%	95% CI[a]	95% CI Miettinen–Nurminen[b]
ATP-11	Azithromycin (N=X)	x	xx	xx, xx	Reference	-	-
	Placebo (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx

N = Number of subjects in the ATP-11 analysis population. n = Number of subjects in ATP-11 population with clinical improvement at D11V.
[a]95% CI obtained from linear regression adjusting for study day of D11V. The rates and difference in rates of clinical improvement presented assume that study day of D11V is 11.
[b]The CI from Miettinen–Nurminen did not adjust for study day of D11V.

Table 25: Analysis of Clinical Improvement on D28V - ITT Analysis Population

Analysis Population	Statistic	Azithromycin (N=X)	Placebo (N=X)
ITT	Subjects with non-missing clinical improvement on D28V – n (%)	x (x)	x (x)
	Subjects with one or more components of clinical improvement imputed on D28V – n (%)	x (x)	x (x)
	Percent rate of clinical improvement on D28V (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
	Difference in rates (percent) of clinical improvement, placebo relative to azithromycin (95% CI)[a]	-	xx (xx, xx)
	Conclusion of non-inferiority of placebo to azithromycin[b]	-	Yes/No

N = Number of subjects in the ITT Population. Multiple imputation was used for missing values.
[a]95% CIs were obtained from linear regression model following multiple imputation adjusting for study day of D28V. The rates and difference in rates of clinical improvement presented assume that study day of D28V is 28.
[b]Non-inferiority of placebo was concluded if the lower bound of the CI for the difference in proportions is greater than -12.5%.

Table 26: Analysis of Clinical Improvement on Day 28 - ATP-28 Analysis Population

[Implementation note: If the lower bound of 95% CI for the difference in rates of clinical improvement is greater than -12.5, annotate the interval with footnote c that states 'Lower bound of confidence interval greater than -12.5% (non-inferiority margin).']

Analysis Population	Treatment Group	Rate of Clinical Improvement			Difference in Rates		
		n	%	95% CI[a]	%	95% CI[a]	95% CI Miettinen–Nurminen
ATP-28	**Azithromycin (N=X)**	x	xx	xx, xx	Reference	-	-
	Placebo (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx

N = Number of subjects in the ATP-28 analysis population. n = Number of subjects in ATP-28 population with clinical improvement at D28V.
[a]95% CI obtained from linear regression adjusting for study day of D28V. The rates and difference in rates of clinical improvement presented assume that study day of D28V is 28.
[b]The CI from Miettinen–Nurminen did not adjust for study day of D28V.

Table 27: Sensitivity Analysis of Clinical Improvement at D5V - ITT Analysis Population

	% Imputed as Success in Azithromycin					
% Imputed as Success in Placebo	**0%**	**20%**	**40%**	**60%**	**80%**	**100%**
0%	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
20%	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
40%	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
60%	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
80%	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
100%	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Note: Values shown are differences in rates of clinical improvement for placebo relative to azithromycin and their 95% CI using linear regression.						

Tables with similar format:

Table 28: Sensitivity Analysis of Clinical Improvement at D11V - ITT Analysis Population

Table 29: Sensitivity Analysis of Clinical Improvement at D28V - ITT Analysis Population

Table 30: Analysis of the Number of Days of Antibiotics Use - ATP-11 Analysis Population

Statistic	Value
Number of days of Antibiotic Use – Mean (95% CI)	
Azithromycin (N=X)	x.x (x.x, x.x)
Placebo (N=X)	x.x (x.x, x.x)
Difference in Means, placebo relative to azithromycin (95% CI)[a]	xx.x (xx.x, xx.x)
P-value[b]	x.xxx
Note: N = Number of subjects in the ATP-11 population in the corresponding treatment group. [a]The difference in means was calculated with azithromycin being the reference and its 95% CI based on t-test. [b]P-value obtained by t-test.	

Table with similar format:

Table 31: Analysis of the Number of Days of Antibiotics Use - ATP-28 Analysis Population

[Implementation Note: Update the footnote to use ATP-28.]

Table 32: Analysis of One or More Return Visits to a Physician's Office or Urgent Care for Persisting or Worsening LRTI

Analysis Population	Statistic	Value
ATP-11	Subjects with one or more return visit to a physician's office or urgent care by D11V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Odds Ratio, placebo relative to azithromycin (95% CI)[a]	x.x (x.xx, x.xx)
	P-value[b]	x.xxx
ATP-28	Subjects with one or more return visit to a physician's office or urgent care by D28V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Odds Ratio, placebo relative to azithromycin (95% CI)[a]	x.x (x.x, x.x)
	P-value[b]	x.xxx

N = Number of subjects in the respective analysis population and treatment group.
[a]95% CI for the odds ratio calculated using the Wald method.
[b]P-value obtained by Fisher's Exact Test.

Table 33: Analysis of One or More Emergency Department Visits for Persisting or Worsening LRTI

Analysis Population	Statistic	Value
ATP-11	Subjects with one or more emergent department visits by D11V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Odds Ratio, placebo relative to azithromycin (95% CI)[a]	x.x (x.x, x.x)
	P-value[b]	x.xxx
ATP-28	Subjects with one or more emergent department visits by D28V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Odds Ratio, placebo relative to azithromycin (95% CI)[a]	x.x (x.x, x.x)
	P-value[b]	x.xxx

N = Number of subjects in the respective analysis population and treatment group.
[a]95% CI for the odds ratio calculated using the Wald method.
[b]P-value obtained by Fisher's Exact Test.

Table 34: Analysis of One or More Hospitalizations for Persisting or Worsening LRTI at Any Time After Randomization

Analysis Population	Statistic	Value
ATP-11	Subjects with one or more hospitalizations by D11V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Odds Ratio, placebo relative to azithromycin (95% CI)[a]	x.x (x.x, x.x)
	P-value[b]	x.xxx
ATP-28	Subjects with one or more hospitalizations by D28V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Odds Ratio, placebo relative to azithromycin (95% CI)[a]	xx.x (xx.x, xx.x)
	P-value[b]	x.xxx

N = Number of subjects in the respective analysis population and treatment group. Only subjects not hospitalized at enrollment or randomization visit will be included.
[a]95% CI for the odds ratio calculated using the Wald method.
[b]P-value obtained by Fisher's Exact Test.

Table 35: Improvement in LRTI Symptoms or Fever at D11V - ATP-11 Analysis Population

Symptom	Azithromycin				Placebo						
	N	n	%	95% CI[a]	N	n	%	95% CI[a]	Difference (95% CI)[b]	Odds Ratio (95% CI)[c]	P-Value[d]
Any Symptom	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Any Symptom or Fever	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
At Least 2 Symptoms or Fever	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Cough	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Sputum Production	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Chest Pain	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Difficulty Breathing	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Fever	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-11 analysis population and the respective treatment group with the symptom of severity of grade 1 or worse symptom or with fever at baseline.
n = Number of subjects with improvement.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]95% CI for the odds ratio, placebo relative to azithromycin, calculated using the Wald method.
[d]P-values obtained by Fisher's Exact Test.

Table with similar format:

Table 36: Improvement in LRTI Symptoms or Fever at D28V - ATP-28 Analysis Population

[Implementation Note: Update the footnote to use ATP-28.]

Table 37: ITT Analysis of DOOR at Day 5 - ITT Analysis Population

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[a]	x.xx (x.xx, x.xx)
P-value[b]	x.xxx

[a]Probability of Higher DOOR in Placebo Arm at D11V + 0.5 Probability of Equal DOOR. 95% CI obtained through inversion of the F-test used to compute the p-value.
[b]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 38: According-to-Protocol Analysis of DOOR at D5V - ATP-5 Analysis Population

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Placebo Arm)[a] (95% CI) [a]	x.xx (x.xx, x.xx)
P-value[b]	x.xxx

[a]Probability of Higher DOOR in Placebo Arm at D11V + 0.5 Probability of Equal DOOR. 95% CI obtained through inversion of the F-test used to compute the p-value.
[b]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 39: Deterioration in LRTI Symptoms at D5V - ATP-5 Analysis Population

Symptom	Azithromycin				Placebo					
	N	n	%	95% CI[a]	N	n	%	95% CI[a]	Difference (95% CI)[b]	P-Value[c]
Any Symptom	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Cough	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Sputum Production	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Chest Pain	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Difficulty Breathing	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group having the symptom at baseline with non-missing severity.
n = Number of subjects with at-least one step deterioration (worsening from mild to moderate for example) in any qualifying symptom regardless whether the symptom was present at enrollment or not.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table with similar format:

Table 40: Deterioration in LRTI Symptoms at D11V - ATP-11 Analysis Population

[Implementation Note: Update the footnote to use ATP-11.]

Table 41: Improvement in Symptom or Vital Sign - ATP-5 Analysis Population

Symptom	Azithromycin				Placebo					
	N	n	%	95% CI[a]	N	n	%	95% CI[a]	Difference (95% CI)[b]	P-Value[c]
Any Symptom or Sign	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Any Symptom	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Any Sign	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
At Least 2 Symptoms or Signs	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Cough	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Sputum Production	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Chest Pain	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Difficulty Breathing	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Temperature	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Pulse	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Respiratory Rate	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group with the symptom or vital sign abnormality present at baseline.
n = Number of subjects with the vital sign abnormality at baseline whose symptom or vital sign improved.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 42: New Occurrence of Vital Sign Abnormality or Presence of Fever at D5V - ATP-5 Analysis Population

Symptom	Azithromycin				Placebo					
	N	n	%	95% CI[a]	N	n	%	95% CI[a]	Difference (95% CI)[b]	P-Value[d]
Any Vital Sign	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Temperature	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Pulse	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Respiratory Rate	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
Fever in the 24 hours preceding or at D5V	x	x	x	(x.x, x.x)	x	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group without the vital sign abnormality at baseline. For fever, N was defined as the total number of subjects with non-missing fever at D5V.
n = Number of subjects with normal vital sign at baseline, but who developed abnormal vital sign at D5V. For fever, n was defined as number of subjects with fever in the 24 hours preceding or at D5V as defined in Section 6.5.1.3.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 43: Any Medically Attended Visit for Persistent or Worsening LRTI - ATP-5 Analysis Population

Symptom	Azithromycin (N=X)			Placebo (N=X)				
	n	%	95% CI[a]	n	%	95% CI[a]	Difference (95% CI)[b]	P-Value[c]
Any MAV	x	x	(x.x, x.x)	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
One or more visits to ED	x	x	(x.x, x.x)	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
One or more visits to an outpatient clinic	x	x	(x.x, x.x)	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
One or more visits to an urgent care center	x	x	(x.x, x.x)	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx
One or more hospitalizations	x	x	(x.x, x.x)	x	x	(x.x, x.x)	xx (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method
[c]P-values obtained by Fisher's Exact Test.

Table with similar format:

Table 44: Any Medically Attended Visit for Persistent or Worsening LRTI - ATP-11 Analysis Population

[Implementation Note: Update the footnote to use ATP-11.]

Table 45: Analysis of Fever in the 24 Hours Preceding or at D11V

Analysis Population	Statistic	Value
ATP-11	Subjects with fever in the 24 hours preceding or at D11V – n (%)	
	Azithromycin (N=X)	x (xx)
	Placebo (N=X)	x (xx)
	Difference in Proportions, placebo relative to azithromycin (95% CI)[a]	xx.x (xx, xx)
	P-value[b]	x.xxx

N = Number of subjects in the respective analysis population and treatment group.
[a]95% CI for the difference in proportions calculated using the Miettinen–Nurminen method.
[b]P-value obtained by Fisher's Exact Test.

Table 46: ITT Analysis of DOOR at D11V - ITT Analysis Population

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[a]	x.xx (x.xx, x.xx)
P-value[b]	x.xxx

[a]Probability of Higher DOOR in Placebo Arm at D11V + 0.5 Probability of Equal DOOR. 95% CI obtained through inversion of the F-test used to compute the p-value.
[b]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 47: According-to-Protocol Analysis of DOOR at D11V - ATP-11 Analysis Population

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[a]	x.xx (x.xx, x.xx)
P-value[b]	x.xxx

[a]Probability of Higher DOOR in Placebo Arm at D11V + 0.5 Probability of Equal DOOR. 95% CI obtained through inversion of the F-test used to compute the p-value.
[b]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 48: According-to-Protocol Analysis of DOOR - Complete Data

Analysis	N	Pr(Higher DOOR)[a]	Normal Approx. 95% CI[b]	P-value[c]
According-to-Protocol (ATP-5)	x	x.xx	x.xx, x.xx	x.xxx
According-to-Protocol (ATP-11)	x	x.xx	x.xx, x.xx	x.xxx

N = Number of subjects with complete data in the given analysis population.
[a]Probability of Higher DOOR in Placebo Arm at D5V (or D11V) + 0.5 Probability of Equal DOOR.
[b]Obtained through the inversion of the Mann-Whitney U test with a normal approximation and using the variance formula in Section 8.2.8 correcting for ties.
[c]P-value obtained by Mann-Whitney U Test.

Table 49: ITT Analysis of Ordinal Clinical Outcome - ITT Analysis Population

Timepoint	Ordinal Clinical Outcome	Azithromycin (N=X)		Placebo (N=X)	
		n	% (95% CI)[1]	n	% (95% CI)[a]
D5V	1	xx	xx (xx, xx)	xx	xx (xx, xx)
	2	xx	xx (xx, xx)	xx	xx (xx, xx)
	3	xx	xx (xx, xx)	xx	xx (xx, xx)
	4	xx	xx (xx, xx)	xx	xx (xx, xx)
	5	xx	xx (xx, xx)	xx	xx (xx, xx)
	6	xx	xx (xx, xx)	xx	xx (xx, xx)
	7	xx	xx (xx, xx)	xx	xx (xx, xx)
	8	xx	xx (xx, xx)	xx	xx (xx, xx)
	Missing	xx	xx (xx, xx)	xx	xx (xx, xx)
D11V	1	xx	xx (xx, xx)	xx	xx (xx, xx)
	2	xx	xx (xx, xx)	xx	xx (xx, xx)
	3	xx	xx (xx, xx)	xx	xx (xx, xx)
	4	xx	xx (xx, xx)	xx	xx (xx, xx)
	5	xx	xx (xx, xx)	xx	xx (xx, xx)
	6	xx	xx (xx, xx)	xx	xx (xx, xx)
	7	xx	xx (xx, xx)	xx	xx (xx, xx)
	8	xx	xx (xx, xx)	xx	xx (xx, xx)
	Missing	xx	xx (xx, xx)	xx	xx (xx, xx)
D28V	1	xx	xx (xx, xx)	xx	xx (xx, xx)
	2	xx	xx (xx, xx)	xx	xx (xx, xx)
	3	xx	xx (xx, xx)	xx	xx (xx, xx)
	4	xx	xx (xx, xx)	xx	xx (xx, xx)
	5	xx	xx (xx, xx)	xx	xx (xx, xx)
	6	xx	xx (xx, xx)	xx	xx (xx, xx)
	7	xx	xx (xx, xx)	xx	xx (xx, xx)
	8	xx	xx (xx, xx)	xx	xx (xx, xx)
	Missing	xx	xx (xx, xx)	xx	xx (xx, xx)

N = Number of subjects in the ITT Population in the given treatment group.
[a]95% CI estimated using the Wilson Method.

Table 50: Analysis of Ordinal Clinical Outcome at D5V - ATP-5 Analysis Population

[Implementation note: The Missing row will be deleted if no subject in the ATP-5 analysis population had missing OCO.]

Ordinal Clinical Outcome	Azithromycin (N=X)		Placebo (N=X)	
	n	% (95% CI)[a]	n	% (95% CI)[a]
1	xx	xx (xx, xx)	xx	xx (xx, xx)
2	xx	xx (xx, xx)	xx	xx (xx, xx)
3	xx	xx (xx, xx)	xx	xx (xx, xx)
4	xx	xx (xx, xx)	xx	xx (xx, xx)
5	xx	xx (xx, xx)	xx	xx (xx, xx)
6	xx	xx (xx, xx)	xx	xx (xx, xx)
7	xx	xx (xx, xx)	xx	xx (xx, xx)
8	xx	xx (xx, xx)	xx	xx (xx, xx)
Missing	xx	xx (xx, xx)	xx	xx (xx, xx)

N = Number of subjects in the ATP-5 Population in the given treatment group.
[a]95% CI estimated using the Wilson Method.

Table with similar format:

Table 51: Analysis of Ordinal Clinical Outcome at D11V - ATP-11 Analysis Population

[Implementation note: The Missing row will be deleted if no subject in the ATP-11 analysis population had missing OCO.]

Table 52: Number of Times Clinical Improvement was Achieved - ITT Analysis Population

Number of Times	Azithromycin (N=X)		Placebo (N=X)	
	n	% (95% CI)[a]	n	% (95% CI)[a]
0	xx	xx (xx, xx)	xx	xx (xx, xx)
1	xx	xx (xx, xx)	xx	xx (xx, xx)
2	xx	xx (xx, xx)	xx	xx (xx, xx)
3	xx	xx (xx, xx)	xx	xx (xx, xx)
Missing[b]	xx	xx (xx, xx)	xx	xx (xx, xx)

N = Number of subjects in the ITT Population in the given treatment group.
[a]95% CI estimated using the Wilson Method.
[b]Number of subjects missing clinical improvement at all three timepoints (D5V, D11V, D28V) will be classified as missing.

Table 53: ITT Analysis of DOOR Based on Number of Times Clinical Improvement was Achieved Across D5V, D11V, and D28V - ITT Analysis Population with Complete Data

Tie-Breaking	Statistic	Value
No tie-breaking	Subjects with non-missing DOOR– n (%)	x (x)
	Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[b]	x.xx (x.xx, x.xx)
	P-value[c]	x.xxx
Duration of antibiotic use as tie-breaker	Subjects with non-missing DOOR– n (%)	x (x)
	Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[b]	x.xx (x.xx, x.xx)
	P-value[c]	x.xxx

Note: DOOR was calculated based on subjects with non-missing clinical improvement for at least one of the timepoints.
[a]Probability of Higher DOOR in Placebo Arm + 0.5 Probability of Equal DOOR. CI obtained through inversion of the F-test used to compute the p-value.
[b]Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance provided in Section 8.2.8 correcting for ties.
[c]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance.

Table 54: ITT Analysis of DOOR Based on Average Ordinal Clinical Outcome from Study Day 1 Through Study Day 11 - ITT Analysis Population with Complete Data

Statistic	Value
Subjects with non-missing DOOR– n (%)	x (x)
Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[b]	x.xx (x.xx, x.xx)
P-value[c]	x.xxx

Note: DOOR was calculated based on subjects with non-missing OCO at atleast one of the timepoints. Missing values were ignored when calculating average OCO.
[a]Probability of Higher DOOR in Placebo Arm + 0.5 Probability of Equal DOOR. CI obtained through inversion of the F-test used to compute the p-value.
[b]Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance provided in Section 8.2.8 correcting for ties.
[c]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance.

Table 55: ITT Analysis of DOOR Based on Average Ordinal Clinical Outcome from D5V, D11V, and D28V - ITT Analysis Population with Complete Data

Statistic	Value
Subjects with non-missing DOOR– n (%)	x (x)
Pr(Higher DOOR in Placebo Arm)[a] (95% CI)[b]	x.xx (x.xx, x.xx)
P-value[c]	x.xxx

Note: DOOR was calculated based on subjects with non-missing OCO at atleast one of the timepoints. Missing values were ignored when calculating average OCO.
[a]Probability of Higher DOOR in Placebo Arm + 0.5 Probability of Equal DOOR. CI obtained through inversion of the F-test used to compute the p-value.
[b]Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance provided in Section 8.2.8 correcting for ties.
[c]P-value obtained by Mann-Whitney U Test. P-value boundary of 0.05 is used to conclude statistical significance.

Table 56: Risk of Mild, Moderate, or Severe Solicited Events from Study Day 1 to D5V - ATP-5 Analysis Population

Symptom	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
	n (%)	95% CI[a]	n (%)	95% CI[a]		
Any Symptom	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group with complete records from study Day 1 to D5V.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 57: Risk of Moderate or Severe Solicited Events from Study Day 1 to D5V - ATP-5 Analysis Population

Symptom	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Any Symptom	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group with complete records from Study Day 1 to D5V.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 58: Risk of Severe Solicited Events from Study Day 1 to D5V - ATP-5 Analysis Population

Symptom	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Any Symptom	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 analysis population and the respective treatment group with complete records from Study Day 1 to D5V.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 59: Risk of Mild, Moderate, or Severe Solicited Events from Study Day 1 to Day 11 - ATP-11 Analysis Population

Symptom	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Any Symptom	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-11 analysis population and the respective treatment group with complete records from Study Day 1 to Day 11.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 60: Risk of Moderate or Severe Solicited Events from Study Day 1 to Day 11 - ATP-11 Analysis Population

Symptom	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Any Symptom	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-11 analysis population and the respective treatment group with complete records from Study Day 1 to Day 11.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 61: Risk of Severe Solicited Events from Study Day 1 to Day 11 - ATP-11 Analysis Population

Symptom	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Any Symptom	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-11 analysis population and the respective treatment group with complete records from Study Day 1 to Day 11.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values obtained by Fisher's Exact Test.

Table 62: Analysis of Mean Changes in PCT Levels - ATP-5 Analysis Population

Clinical Status	Time Point	Statistic	Azithromycin (N=X)	Placebo (N=X)	Difference in Mean PCT Changes, Placebo Relative to Azithromycin (95% CI) [b]	P-value[c]
Clinical Improvement	Baseline	n	x	x	--	--
		Mean (SD)	x.x (x.x)	x.x (x.x)	--	--
		Median	x.x (x.x)	x.x (x.x)	--	--
		Range (Min, Max)	x.x (x.x)	x.x (x.x)	--	--
	D5V	n	x	x	--	--
		Mean (SD)	x.x (x.x)	x.x (x.x)	--	--
		Median	x.x (x.x)	x.x (x.x)	--	--
		Range (Min, Max)	x.x (x.x)	x.x (x.x)	--	--
		Mean PCT Changes from Baseline (95% CI)[a]	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.xxx
Clinical Failure	Baseline	n	x	x	--	--
		Mean (SD)	x.x (x.x)	x.x (x.x)	--	--
		Median	x.x (x.x)	x.x (x.x)	--	--
		Range (Min, Max)	x.x (x.x)	x.x (x.x)	--	--
	D5V	n	x	x	--	--
		Mean (SD)	x.x (x.x)	x.x (x.x)	--	--
		Median	x.x (x.x)	x.x (x.x)	--	--
		Range (Min, Max)	x.x (x.x)	x.x (x.x)	--	--
		Mean PCT Changes from Baseline (95% CI)[a]	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.xxx
All Subjects	Baseline	n	x	x	--	--
		Mean (SD)	x.x (x.x)	x.x (x.x)	--	--
		Median	x.x (x.x)	x.x (x.x)	--	--
		Range (Min, Max)	x.x (x.x)	x.x (x.x)	--	--

Table 62: Analysis of Mean Changes in PCT Levels - ATP-5 Analysis Population (Continued)

Clinical Status	Time Point	Statistic	Azithromycin (N=X)	Placebo (N=X)	Difference in Mean PCT Changes, Placebo Relative to Azithromycin (95% CI) [b]	P-value[c]
	D5V	n	x	x	--	--
		Mean (SD)	x.x (x.x)	x.x (x.x)	--	--
		Median	x.x (x.x)	x.x (x.x)	--	--
		Range (Min, Max)	x.x (x.x)	x.x (x.x)	--	--
		Mean PCT Changes from Baseline (95% CI)[a]	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the ATP-5 population in the corresponding treatment group. n = Number of subjects in the ATP-5 population with data at the corresponding time point, clinical status, and treatment group.
All PCT values reported as '< x.xx' were imputed to '0.5*x.xx' for analysis.
[a]95% CI for the mean PCT changes from baseline calculated using the 2.5th and 97.5th percentiles of PCT changes from baseline using Bootstrap.
[b]95% CI for the difference in mean PCT changes calculated using the 2.5th and 97.5th percentiles of the difference in mean PCT changes using Bootstrap.
[c]P-value obtained by Wilcoxon Test.

Table 63: Logistic Regression Model to Evaluate the Relationship of Change in Mean PCT Levels at D5V with Clinical Improvement Adjusting for Treatment Group - ATP-5 Analysis Population

Model Parameter	Parameter Category	Parameter Estimate	Standard Errors	Odds Ratio (95% CI)	P-value
Intercept	NA	x.x	x.xx	-	x.xxx
Change in Mean PCT from Baseline	NA	x.x	x.xx	x.x (x.xx, x.xx)	x.xxx
Treatment Group	Azithromycin	-	-	-	-
	Placebo	x.x	x.xx	x.x (x.xx, x.xx)	x.xxx
Centered Study Day of D5V	NA	x.x	x.xx	x.x (x.xx, x.xx)	x.xxx

N = Number of subjects in the ATP-5 population.
The parameter estimate for change in mean PCT from baseline is interpreted as the expected change in log odds of clinical improvement for a one-unit increase in change in Mean PCT from baseline given study day of D5V is 5.

Table 64: Logistic Regression Model to Evaluate the Relationship of PCT Level at Screening with Detection of a Viral or Bacterial Pathogen

Pathogen Type	Model Parameter	Parameter Category	Parameter Estimate	Standard Errors	Odds Ratio (95% CI)	P-value
Viral	Intercept	NA	x.x	x.xx	-	x.xxx
	PCT Level at Screening	NA	x.x	x.xx	x.x (x.xx, x.xx)	x.xxx
Bacterial	Intercept	NA	x.x	x.xx	-	x.xxx
	PCT Level at Screening	NA	x.x	x.xx	x.x (x.xx, x.xx)	x.xxx
Note: This analysis included all subjects, randomized and non-randomized, with non-missing PCT level at screening and non-missing pathogen detection data.						

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.1.1 Solicited Adverse Events

Table 65: Number and Percentage of Subjects Experiencing Solicited Events with 95% CIs by Symptom and Treatment Group - Safety Population

Symptom	Azithromycin (N=X)			Placebo (N=X)		
	n	%	95% CI[a]	n	%	95% CI[a]
Any Symptom	x	xx	x, x	x	xx	x, x
Abdominal pain						
Vomiting						
Diarrhea						
Allergic Reaction						
Candidiasis						

N = Number of subjects in the Safety Population in the respective treatment group who have solicited data reported. Severity of the maximum severity reported post dosing for each subject.
[a]95% CI for proportions calculated using the Wilson method.

Table 66: Number and Percentage of Subjects Experiencing Solicited Events with 95% CIs by Symptom, Maximum Severity, and Treatment Group - Safety Population

Symptom	Severity	Azithromycin (N=X)			Placebo (N=X)		
		n	%	95% CI[a]	n	%	95% CI[a]
Any Symptom	None	x	xx	x, x	x	xx	x, x
	Mild						
	Moderate						
	Severe						
Abdominal pain	None						
	Mild						
	Moderate						
	Severe						
Vomiting	None						
	Mild						
	Moderate						
	Severe						
Diarrhea	None						
	Mild						
	Moderate						
	Severe						
Allergic Reaction	None						
	Mild						
	Moderate						
	Severe						
Candidiasis	None						
	Mild						
	Moderate						
	Severe						

N = Number of subjects in the Safety Population in the respective treatment group who have solicited data reported. Severity of the maximum severity reported post dosing for each subject.
[a]95% CI for proportions calculated using the Wilson method.

Table 67: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing - Azithromycin Group, Safety Population

		Azithromycin											
		Day 1 (N = X)	Day 2 (N = X)	Day 3 (N = X)	Day 4 (N = X)	Day 5 (N = X)	Day 6 (N = X)	Day 7 (N = X)	Day 8 (N = X)	Day 9 (N = X)	Day 10 (N = X)	Day 11 (N = X)	Any Post Dose (N = X)
Symptom	**Severity**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Symptom	None	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Mild												
	Moderate												
	Severe												
	Not Reported												
Abdominal Pain	None	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Mild												
	Moderate												
	Severe												
	Not Reported												
Vomiting	None												
	Mild												
	Moderate												
	Severe												
	Not Reported												
Diarrhea	None												
	Mild												
	Moderate												
	Severe												
	Not Reported												

Table 67: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing - Azithromycin Group, Safety Population (Continued)

		Azithromycin											
		Day 1 (N = X)	Day 2 (N = X)	Day 3 (N = X)	Day 4 (N = X)	Day 5 (N = X)	Day 6 (N = X)	Day 7 (N = X)	Day 8 (N = X)	Day 9 (N = X)	Day 10 (N = X)	Day 11 (N = X)	Any Post Dose (N = X)
Symptom	**Severity**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Allergic Reaction	None	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Mild												
	Moderate												
	Severe												
	Not Reported												
Candidiasis	None												
	Mild												
	Moderate												
	Severe												
	Not Reported												

N = Number of subjects in the Safety Population in the respective treatment group who have solicited data reported on the corresponding day. Severity is the maximum severity reported post dosing for each subject for each day.

Table 68: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing - Placebo Group, Safety Population

		Placebo											
		Day 1 (N = X)	Day 2 (N = X)	Day 3 (N = X)	Day 4 (N = X)	Day 5 (N = X)	Day 6 (N = X)	Day 7 (N = X)	Day 8 (N = X)	Day 9 (N = X)	Day 10 (N = X)	Day 11 (N = X)	Any Post Dose (N = X)
Symptom	**Severity**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Symptom	None	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Mild												
	Moderate												
	Severe												
	Not Reported												
Abdominal Pain	None	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Mild												
	Moderate												
	Severe												
	Not Reported												
Vomiting	None												
	Mild												
	Moderate												
	Severe												
	Not Reported												
Diarrhea	None												
	Mild												
	Moderate												
	Severe												
	Not Reported												

Table 68: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing - Placebo Group, Safety Population (Continued)

		Placebo											
		Day 1 (N = X)	Day 2 (N = X)	Day 3 (N = X)	Day 4 (N = X)	Day 5 (N = X)	Day 6 (N = X)	Day 7 (N = X)	Day 8 (N = X)	Day 9 (N = X)	Day 10 (N = X)	Day 11 (N = X)	Any Post Dose (N = X)
Symptom	**Severity**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Allergic Reaction	None	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Mild												
	Moderate												
	Severe												
	Not Reported												
Candidiasis	None												
	Mild												
	Moderate												
	Severe												
	Not Reported												

N = Number of subjects in the Safety Population in the respective treatment group who have solicited data reported for the corresponding day. Severity is the maximum severity reported post dosing for each subject for each day.

Table 69: Number and Percentage of Subjects Experiencing Solicited Adverse Events of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group - Safety Population

Symptom	Severity	Azithromycin (N=X)		Placebo (N=X)		Risk Difference (95% CI)[b]	P-Value[c]
		n (%)	95% CI[a]	n (%)	95% CI[a]		
Any Symptom	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Abdominal Pain	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

N = Number of subjects in the Safety population who have solicited data reported.
[a]95% CI for proportions calculated using the Wilson method.
[b]95% CI for the difference in proportions, placebo relative to azithromycin, calculated using the Miettinen–Nurminen method.
[c]P-values from Fisher's exact test.

14.3.1.2 Unanticipated Adverse Device Effects

Table 70: Unanticipated Adverse Device Effects by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group

			Azithromycin (N = X)						Placebo (N = X)						All Subjects (N = X)					
			Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
MedDRA System Organ Class	Preferred Term	Severity	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the Safety Population.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 71: Listing of Unanticipated Adverse Device Effects - Safety Population

Adverse Event	Date of PCT Screening Test	No. of Days Post Associated PCT Test (Duration)	Reason Reported as an UADE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:											
Comments:											
Subject ID: , Treatment Group: , AE Number:											
Comments:											

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Not applicable.

14.3.5 Displays of Laboratory Results

Not applicable.

14.3.6 Displays of Vital Signs

Table 72: Summary of Vital Signs by Visit and Treatment Group

		Enrollment Visit		D5V	
		Azithromycin	Placebo	Azithromycin	Placebo
Temperature (C)	N	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx
Respiratory Rate (breaths/min.)	N	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx
Pulse Rate (beats/min.)	N	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx
Diastolic Blood Pressure (mmHg)	N	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx
Systolic Blood Pressure (mmHg)	N	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx
Oxygen Saturation (%)	N	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx
N = Number of subjects in the Safety Population without missing values for a given parameter at a given visit.					

14.4 Summary of Concomitant Medications

Table 73: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Azithromycin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

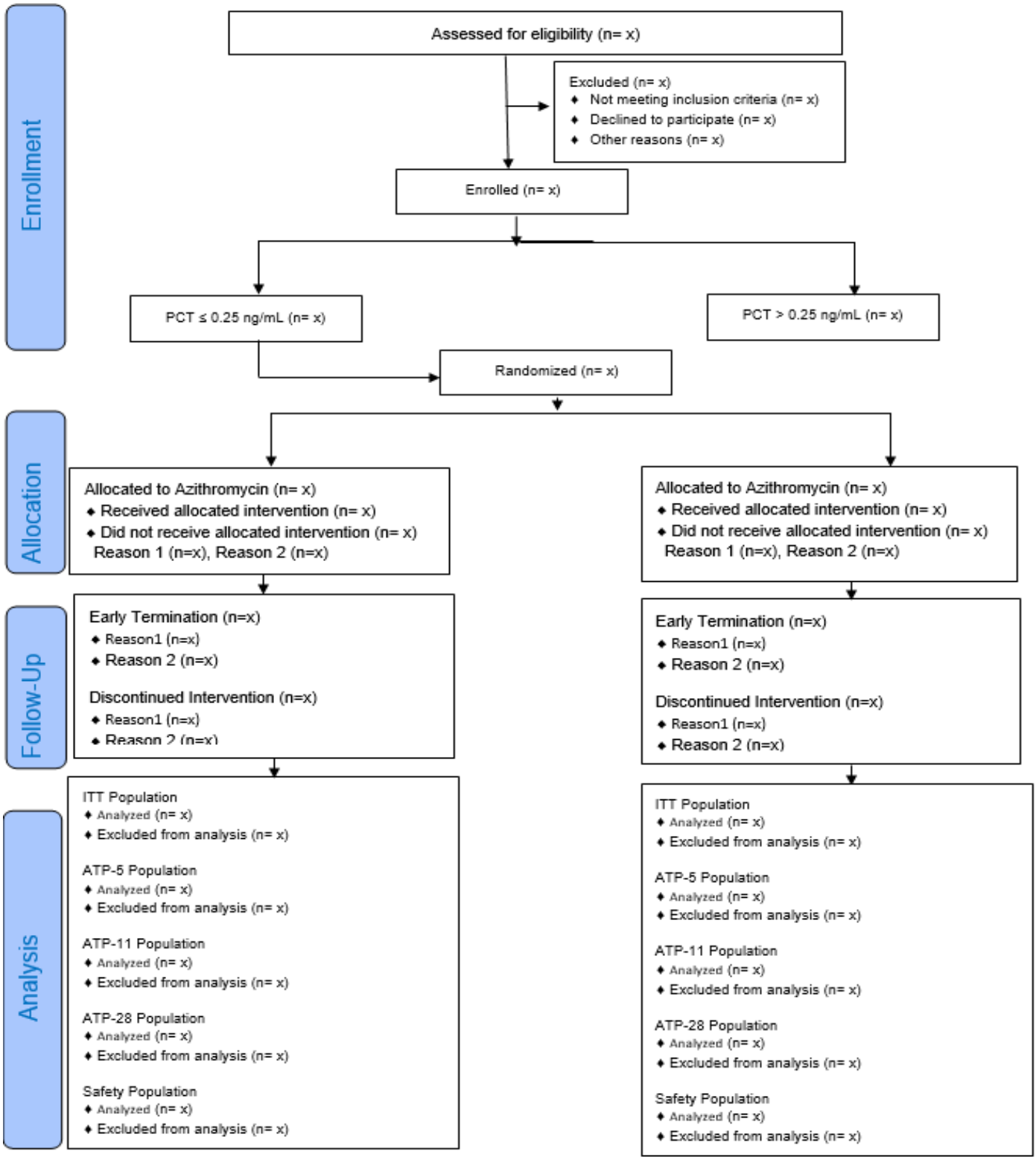
N = Number of subjects in the Safety Population. n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

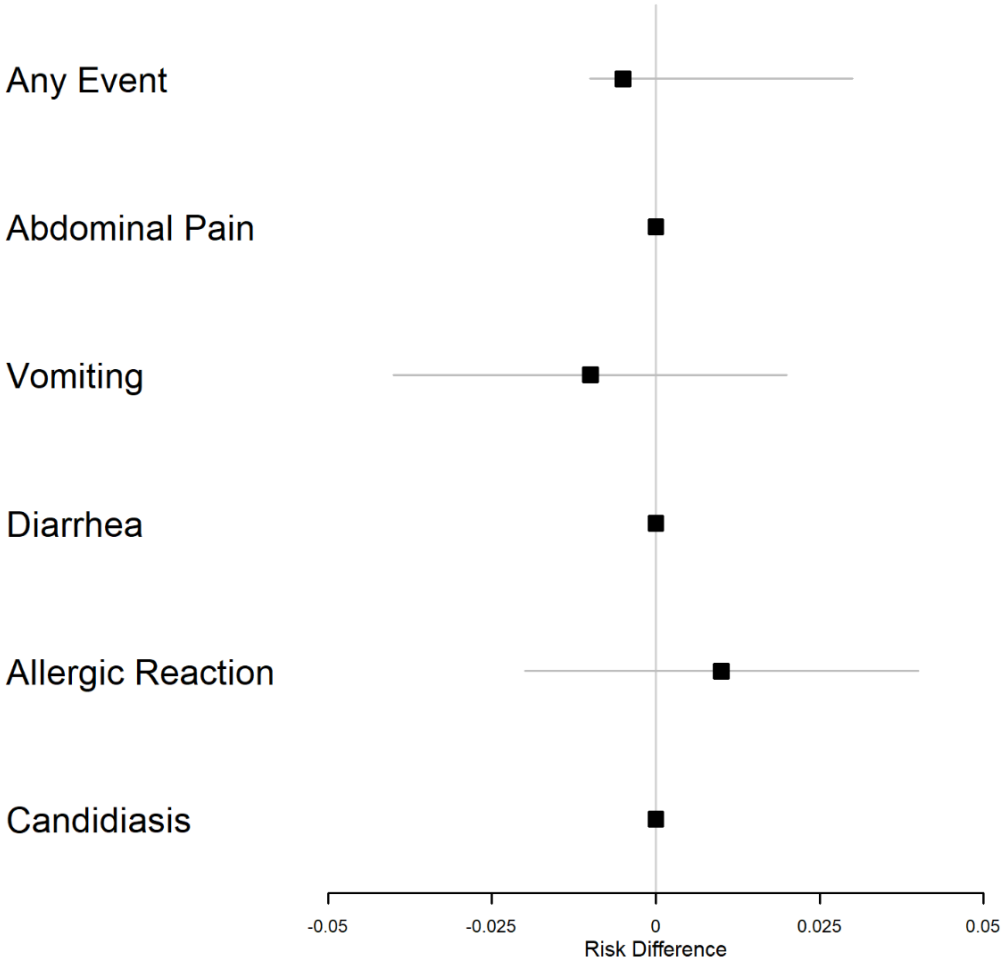
10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram



14.2.2 Efficacy Response Figures by Measure, Treatment, and Time Point

Figure 2: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Solicited Events from Day 1 to D5V of Grade Mild, Moderate, or Severe - ATP-5 Population



Figures with similar format:

Figure 3: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Solicited Events from Day 1 to D5V of Grade Moderate or Severe - ATP-5 Population

Figure 4: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Solicited Events from Day 1 to D5V of Grade Severe - ATP-5 Population

Figure 5: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Solicited Events on from Day 1 to D11V of Grade Mild, Moderate, or Severe - ATP-11 Population

Figure 6: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Solicited Events from Day 1 to D11V of Grade Moderate or Severe - ATP-11 Population

Figure 7: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Solicited Events on from Day 1 to D11V of Grade Severe - ATP-11 Population

Figure 8: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Any Medically Attended Visit for Persisting or Worsening LRTI at Any Time After Randomization - ATP-5 Population

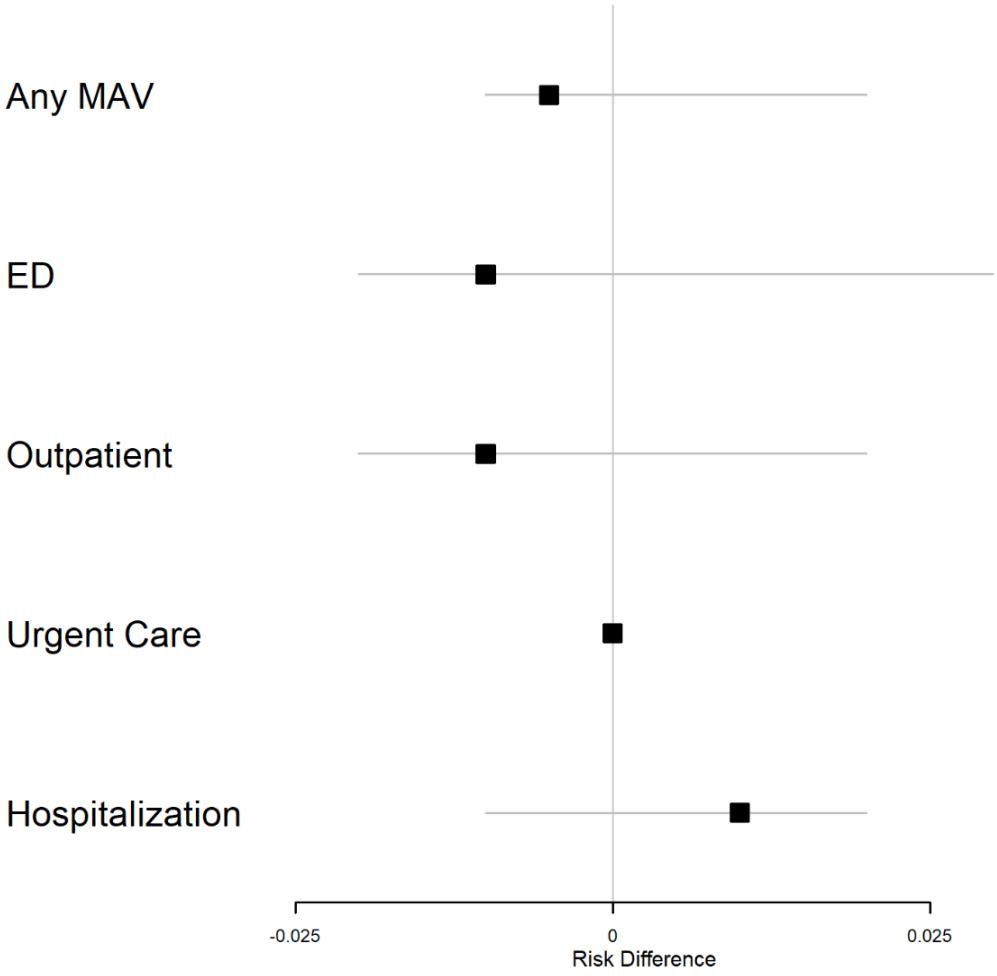


Figure with similar format:

Figure 9: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Any Medically Attended Visit for Persisting or Worsening LRTI at Any Time After Randomization - ATP-11 Population

Figure 10: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Improvement in the Symptom or Sign on Day 5 - ATP-5 Population

Implementation Note: Add a note at the bottom of the figure: 'Cough, Sputum Production, Chest Pain, and Difficulty Breathing are LRTI symptoms while temperature, pulse, and respiratory rate are vital signs used for defining clinical improvement.]

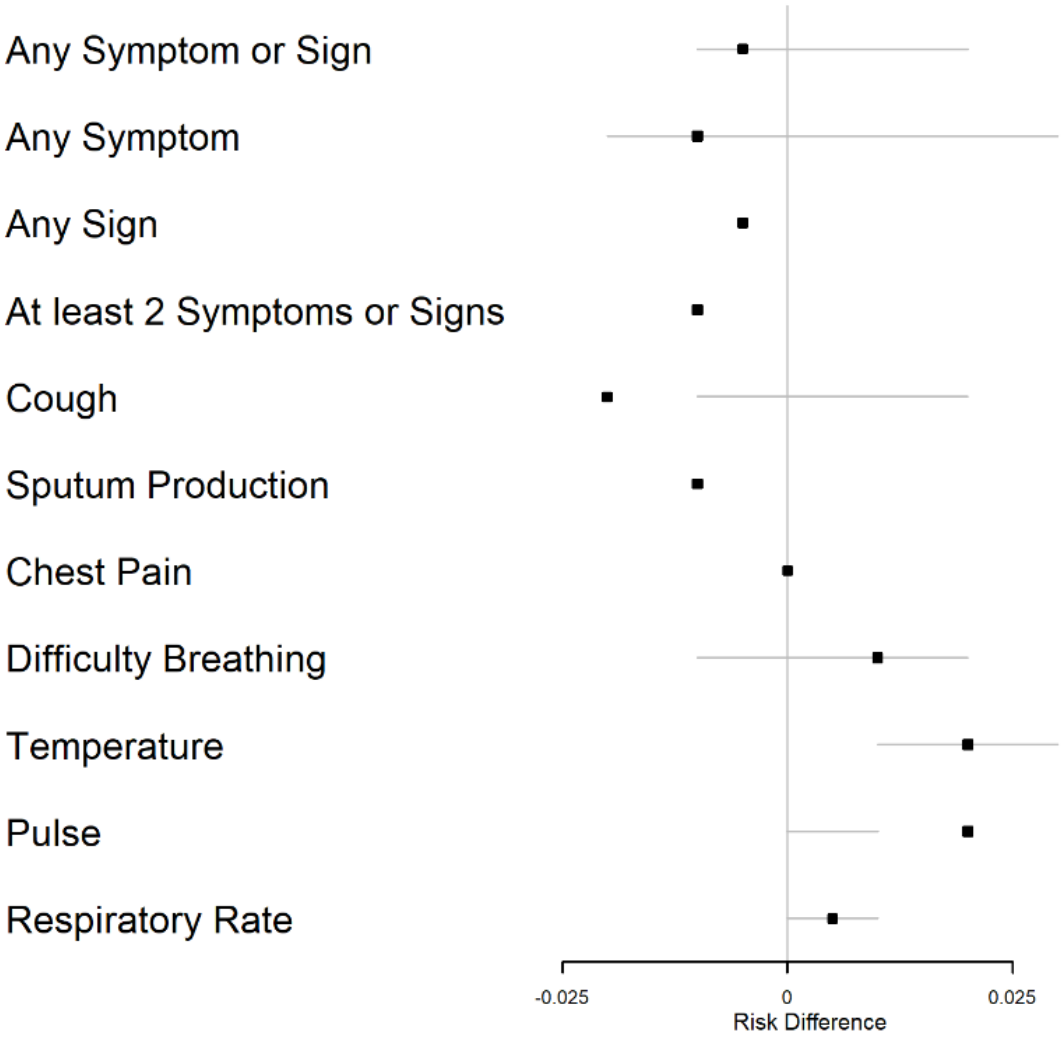


Figure 11: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Improvement in the Symptom or Fever on Day 11 - ATP-11 Population

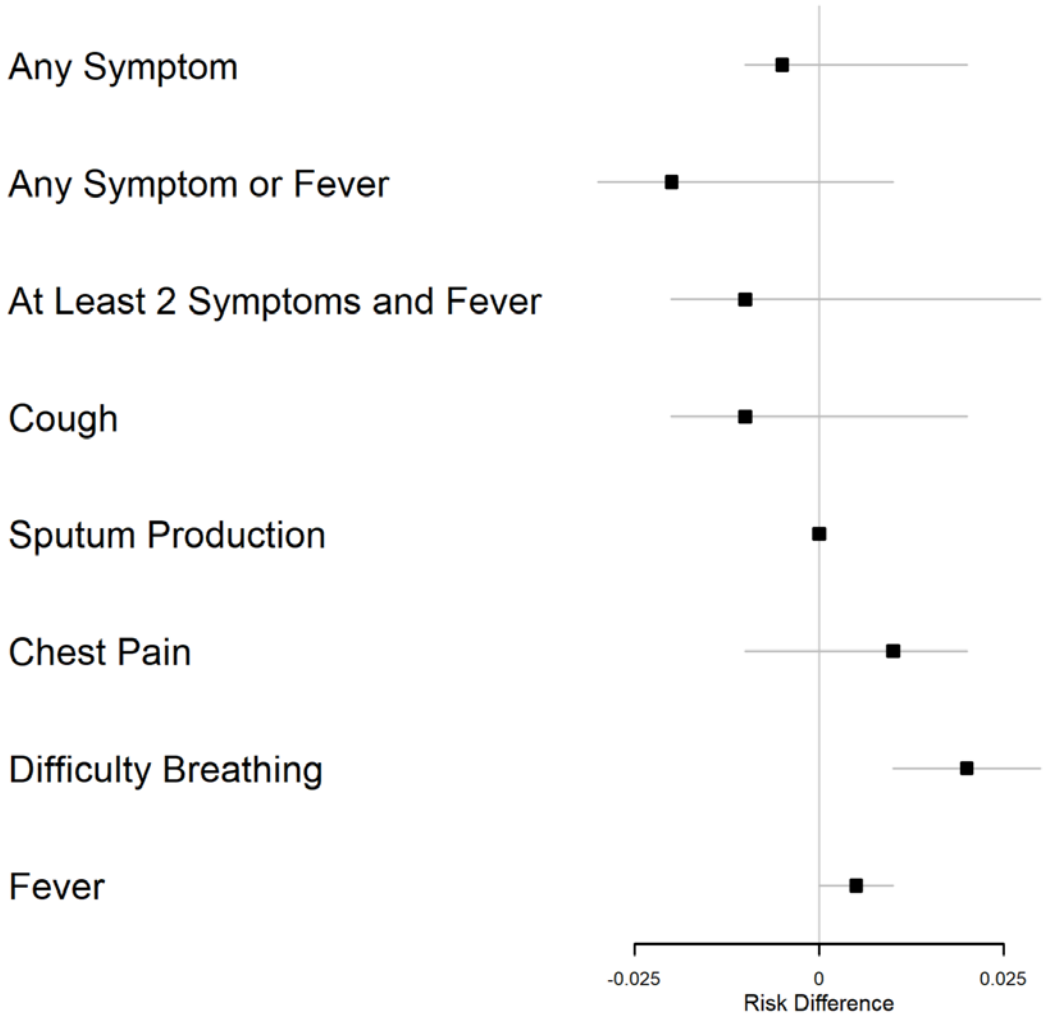


Figure 12: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Deterioration in the Symptom or Sign on Day 5 - ATP-5 Population

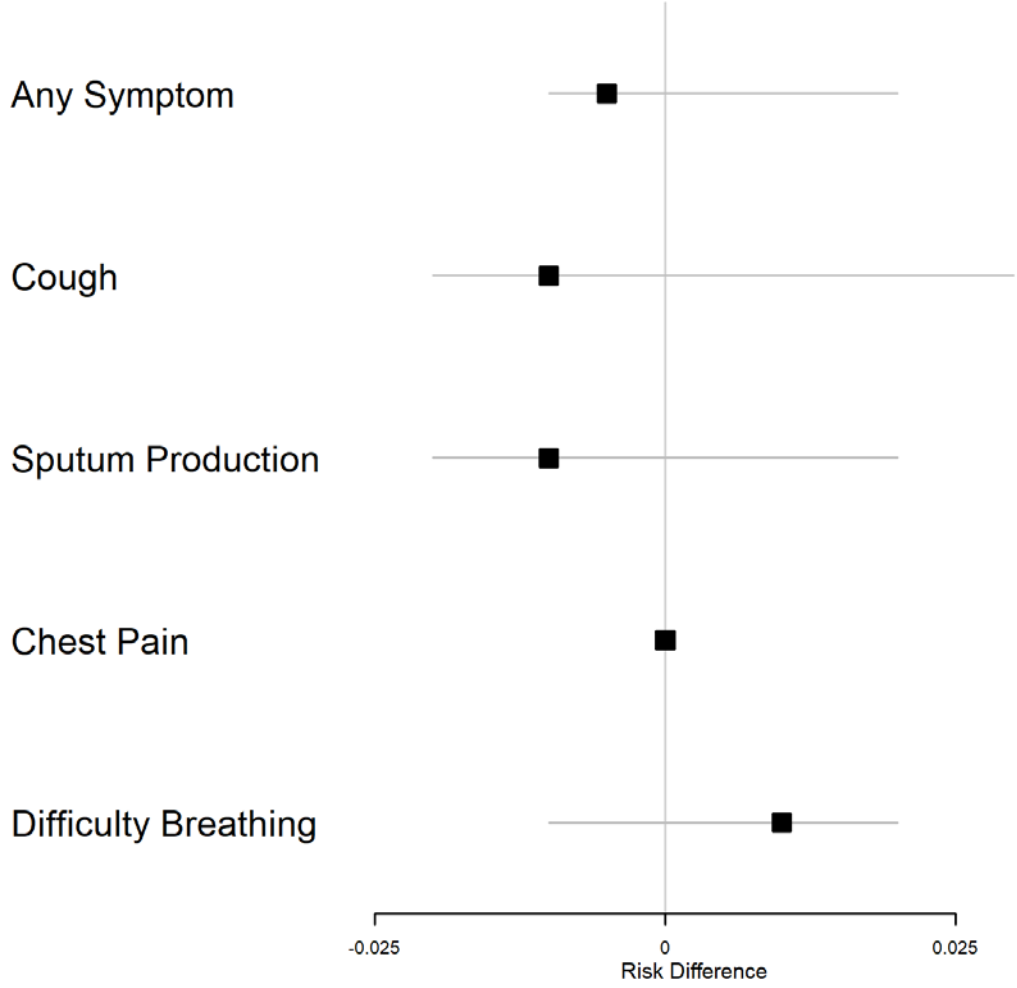


Figure with similar format:

Figure 13: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Deterioration in the Symptom or Sign on Day 11 - ATP-11 Population

Figure 14: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of New Occurrence of Vital Sign Abnormality on Day 5 - ATP-5 Population

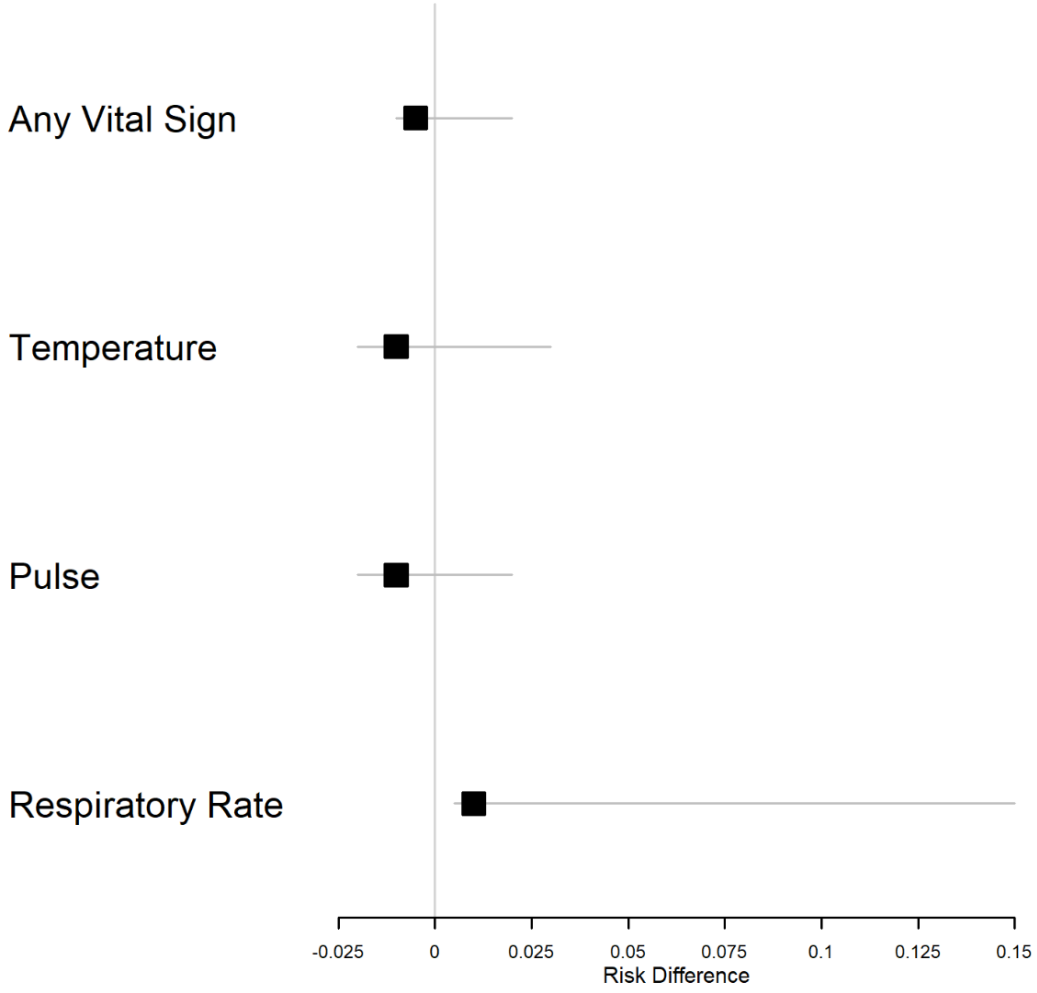


Figure 15: Forest Plot of Risk Difference, Placebo Group Relative to Azithromycin, of Fever on Day 11 - ATP-11 Population

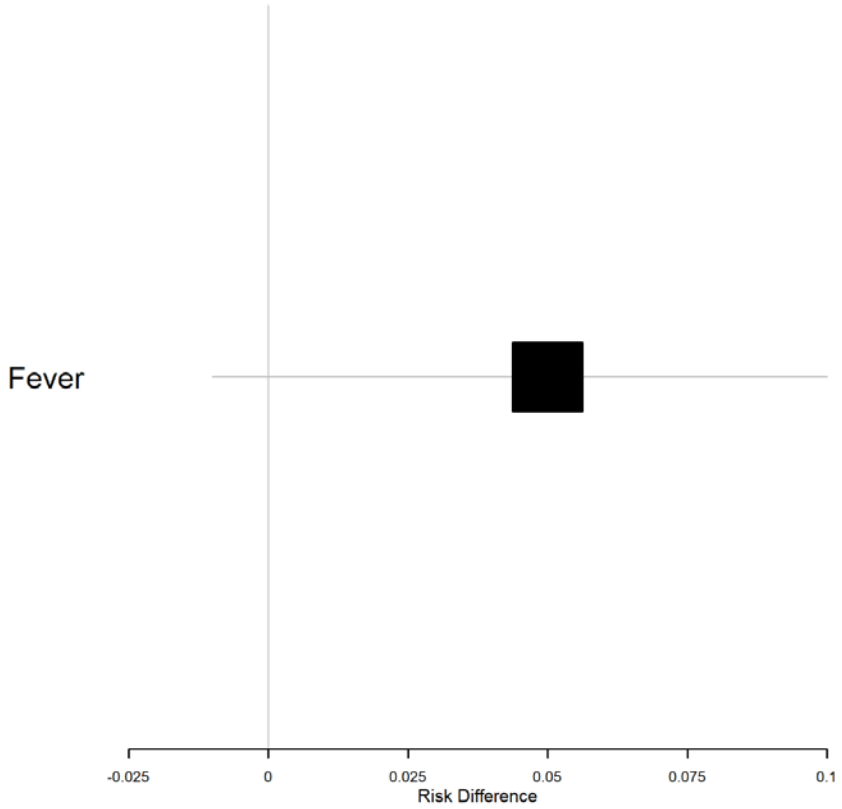


Figure 16: Distribution of Ordinal Clinical Outcome Used for DOOR by Treatment Group and Timepoint

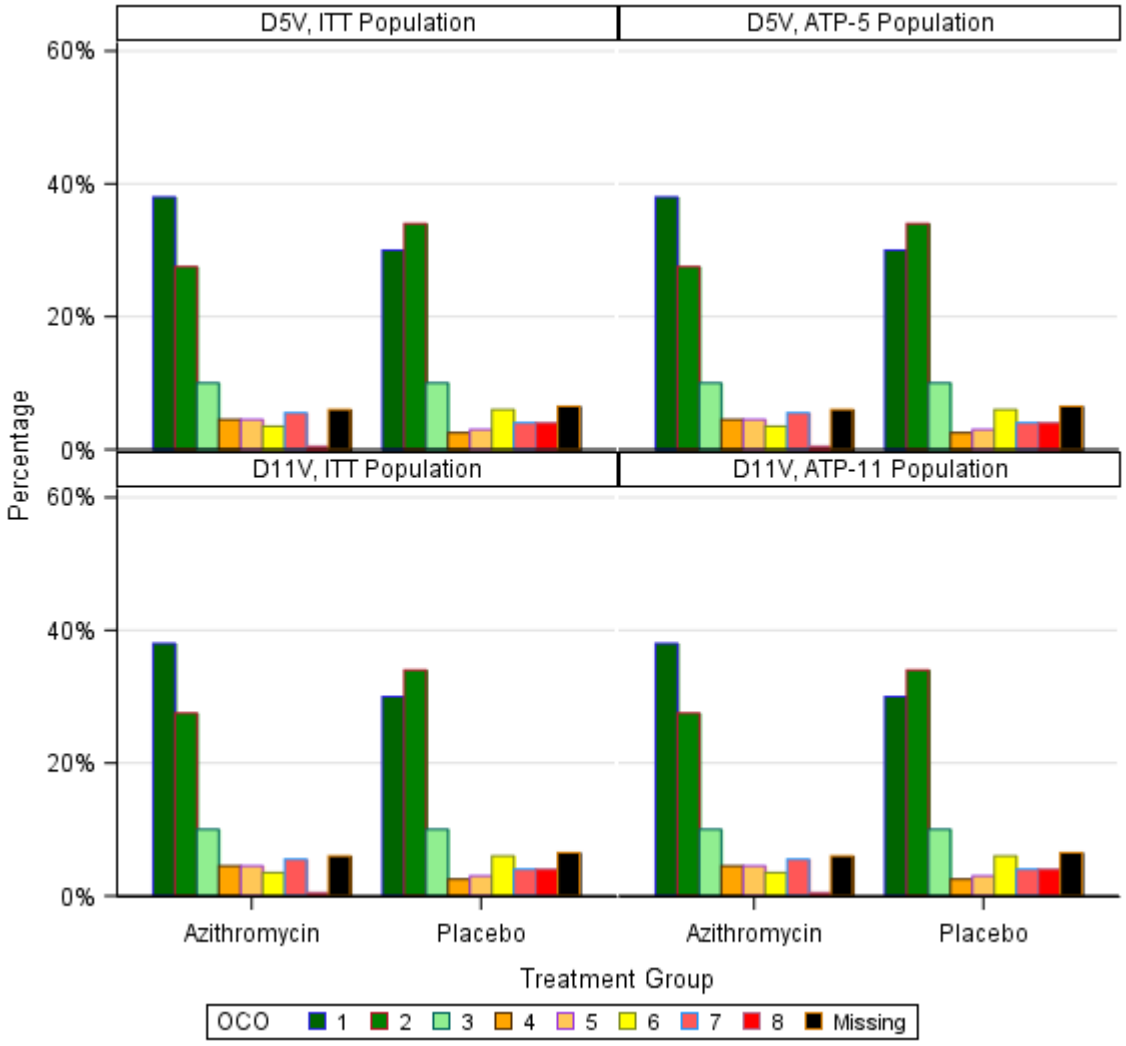
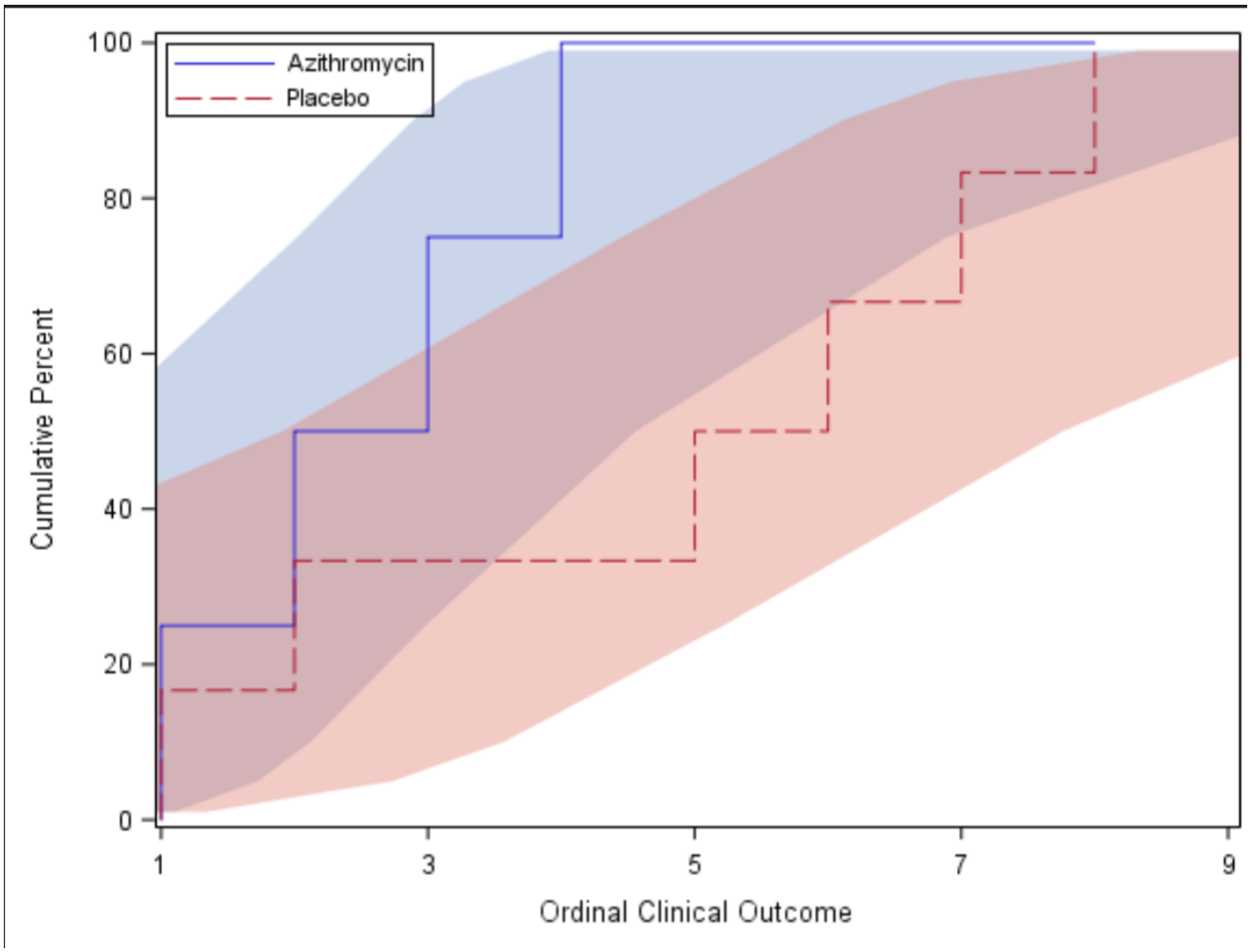


Figure 17: Cumulative Distribution Function for Ordinal Clinical Outcome Used for DOOR by Treatment Group at D5V - ITT Population

[Implementation note: Subjects with missing OCO will be excluded from this plot. 95% confidence bands will be added to the plot. Pseudocode: ***https://communities.sas.com/t5/SAS-Programming/Add-upper-and-lower-confidence-limit-CDF-curves/m-p/316651#M69236****]*



Figures with similar format:

Figure 18: Cumulative Distribution Function for Ordinal Clinical Outcome Used for DOOR by Treatment Group at D5V - ATP-5 Population

Figure 19: Cumulative Distribution Function for Ordinal Clinical Outcome Used for DOOR by Treatment Group at D11V - ITT Population

Figure 20: Cumulative Distribution Function for Ordinal Clinical Outcome Used for DOOR by Treatment Group at D11V - ATP-11 Population

Figure 21: Bivariate Analysis of DOOR at D5V - ITT Analysis Population with Complete Data at D5V

[Implementation Note: This figure will have 4 panels; the rows will represent the number of bootstrap samples (1000, 2000) and the columns will represent the parametric vs non-parametric approach. The ellipse function from the CAR package will be used to estimate the confidence regions using the parametric method and the distfree.cr R package for the distribution free approach will be used to estimating confidence regions. Marginal distributions of difference in duration of antibiotics use and DOOR probability will be added to the plot. This figure will be generated only if the variability in the number of days of antibiotic use justifies making such a figure.]

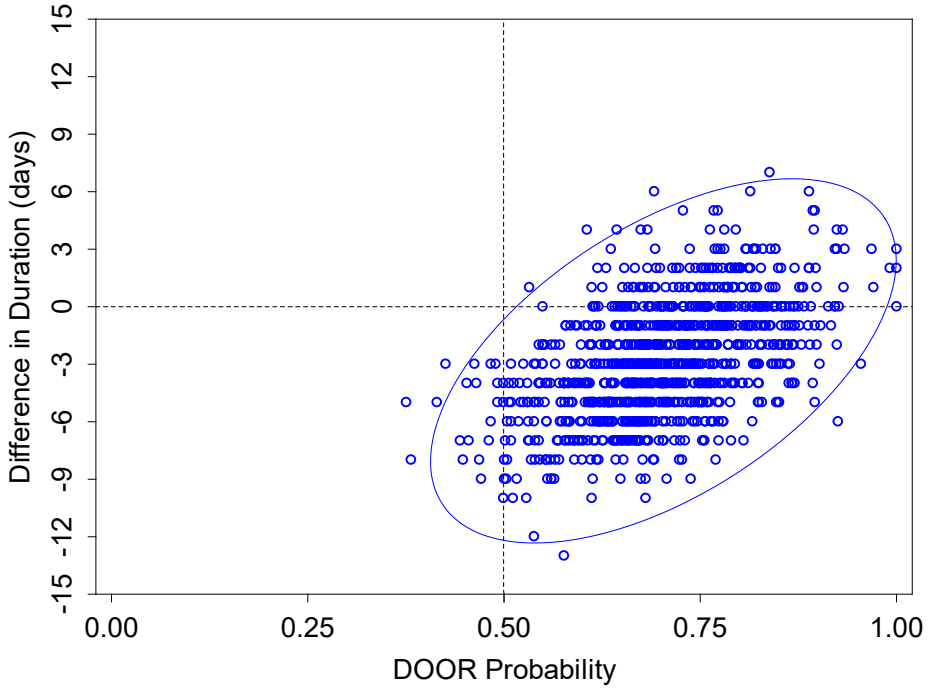


Figure with similar format:

Figure 22: Bivariate Analysis of DOOR at D11V - ITT Analysis Population with Complete Data at D11V

Figure 23: Distribution of Daily Ordinal Clinical Outcomes from Study Day 1 to Study Day 11 by Treatment Group and Timepoint - ITT Population

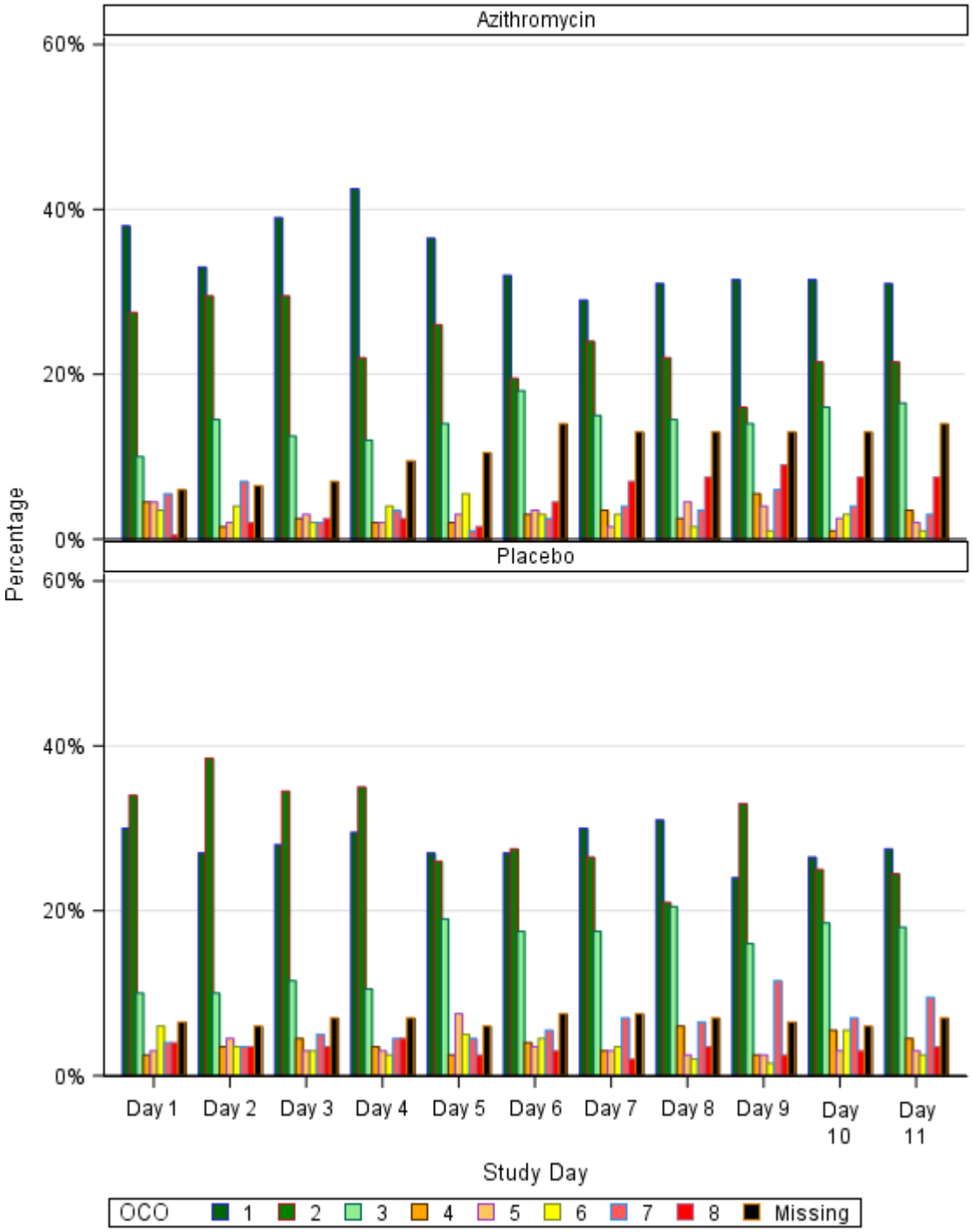


Figure 24: Distribution of Ordinal Clinical Outcomes by Treatment Group at D5V, D11V, and D28V - ITT Population

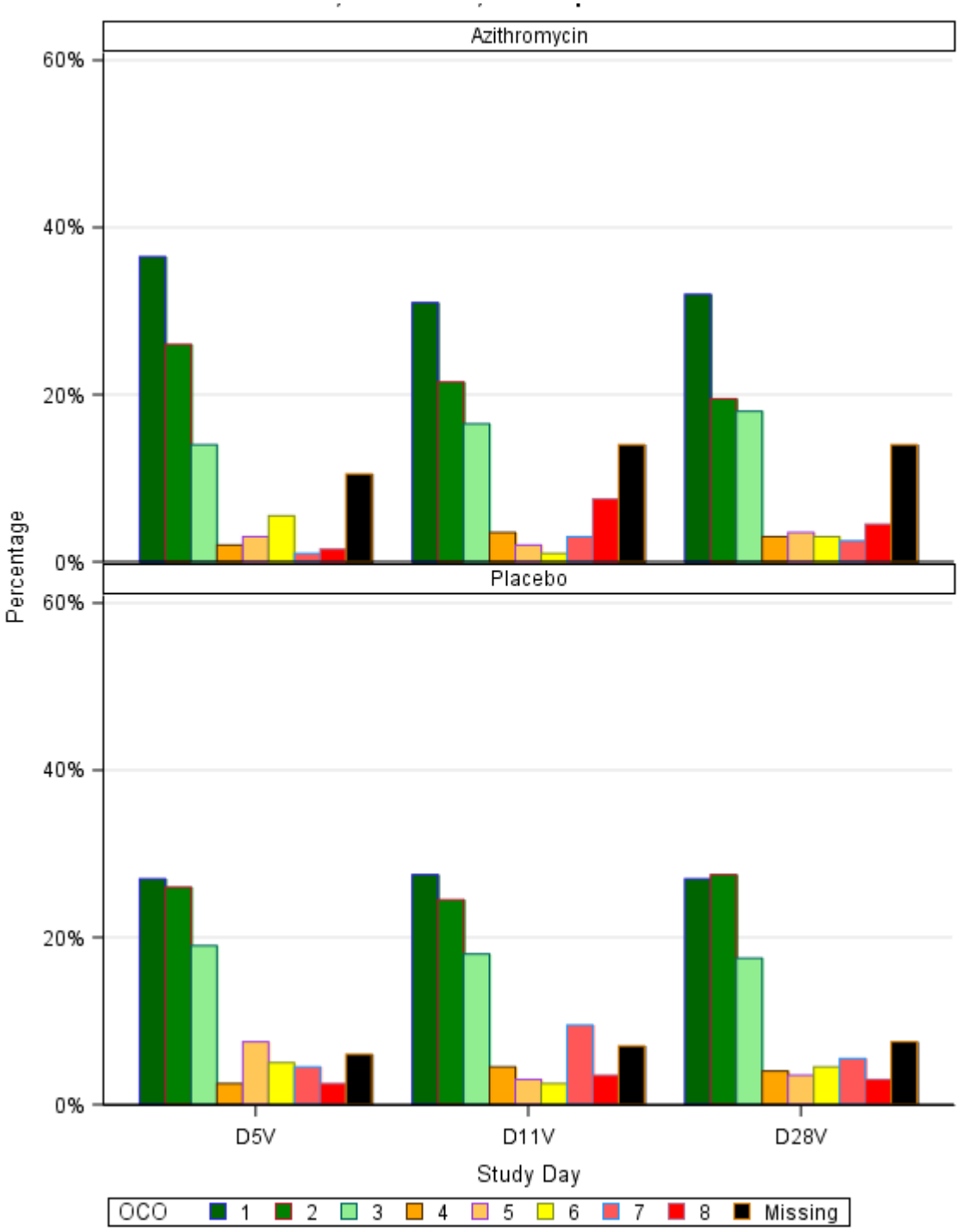


Figure 25: Heatmap of Individual Subjects' Ordinal Clinical Outcomes by Treatment Group from Study Day 1 through Study Day 11 - ITT Population

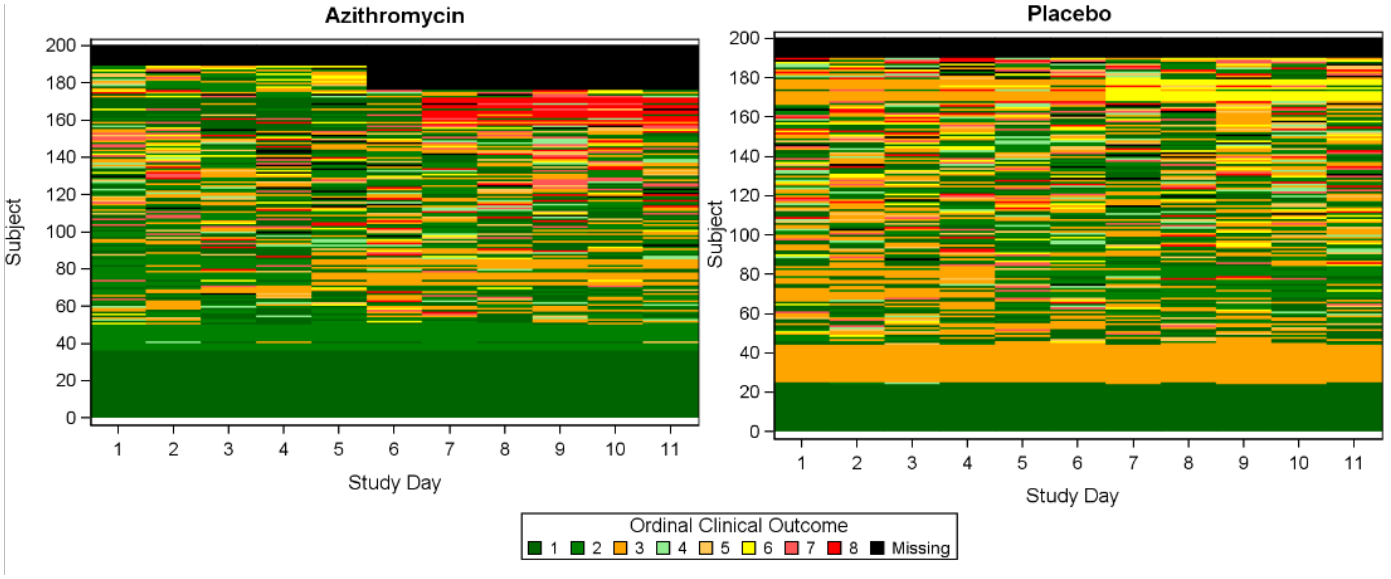
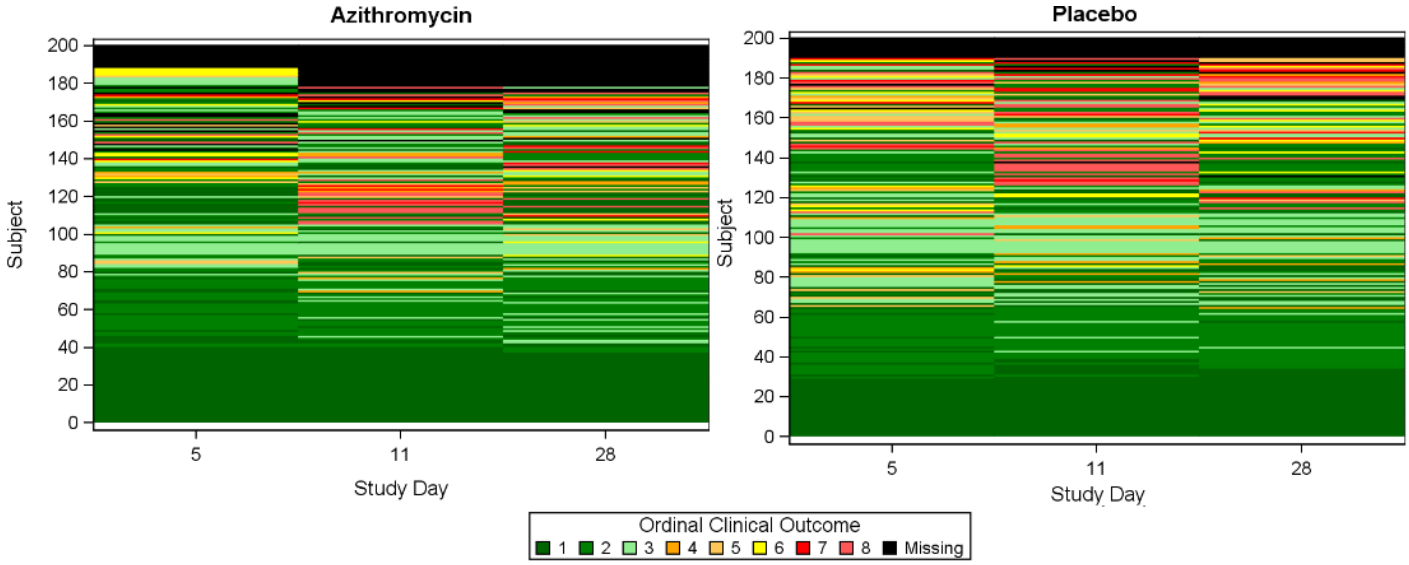


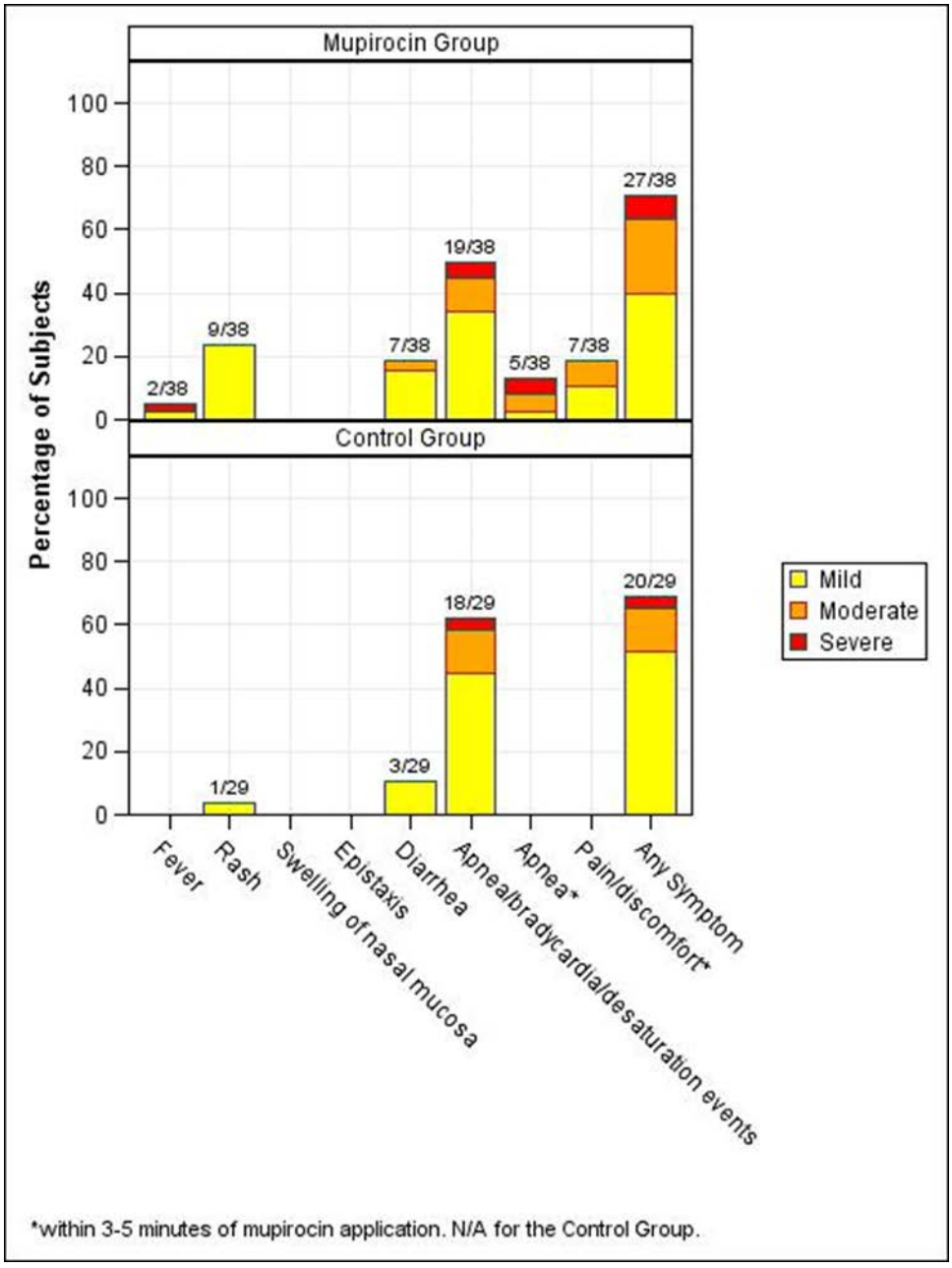
Figure 26: Heatmap of Individual Subjects' Ordinal Clinical Outcomes by Treatment Group at D5V, D11V, and D28V - ITT Population



14.3.1.1 Solicited Adverse Events

Figure 27: Maximum Severity of Solicited Adverse Events by Symptom and Treatment Group

[Programming Note: This figure will present maximum severity of solicited events separately by treatment group. The mockup is an example only. The actual figure will contain treatment groups and solicited events relevant to the 15-0020 protocol.]



14.3.5 Displays of Laboratory Results

Not applicable.

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **16.1.6: Listing of Subjects Receiving Investigational Product**

[Implementation Note: This listing will only include subjects who received at least one dose of study product.]

Subject ID	Treatment Received	Date of First Dose	Date of Last Dose

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 16.2.1: Early Terminations or Discontinued Subjects

[Implementation Note: Category will be either "Early Termination" or "Treatment Discontinuation." In the "Reason" column, concatenate any "specify" fields, including AE number and DV number. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, alphabetically by Category (in the case a subject both terminates early and discontinues treatment).]

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day	Number of Doses Received

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Subject-Specific Protocol Deviations

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Subject refusal." In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: PCT Cohort, Treatment Group, Subject ID, DV Number.]

PCT Cohort	Treatment Group	Subject ID	DV Number	Deviation	Deviation Category	Study day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing 4: 16.2.2.2: Non-Subject-Specific Protocol Deviations

[Implementation Note: In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Subject refusal." Sort order: Site, Start Date.]

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Subjects Excluded from Analysis Populations

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID.]

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Reason Subject Excluded
Azithromycin	SST.XXXX	Safety, ITT, ATP-5, ATP-11, ATP-28	-	-
Azithromycin	SST.XXXX	Safety, ITT, ATP-5	ATP-11	Subject did not complete D11V
			ATP-28	D28V occurred out of the protocol defined window of Day 28 ± 2 days

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographic Data

[Implementation Note: If a subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)." For studies in infants and young children, it may be more appropriate to use weeks or months for age at enrollment. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: PCT Cohort, Treatment Group, Subject ID.]

PCT Cohort	Treatment Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: PCT Cohort, Treatment Group, Subject ID, MH Number.]

PCT Cohort	Treatment Group	Subject ID	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data (if available)

Listing 8: 16.2.5: Treatment Compliance

[Implementation Note: In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, Number of Doses Taken.]

Treatment Group	Subject ID	Number of Doses Taken	Number of Doses Missed[a]

Note: Treatment compliance implies that a subject received 5 doses of study product.
[a]Total expected number of doses is 5.

16.2.6 Adverse Events

Listing 9: 16.2.6: Solicited Events

[Implementation Note: This listing is not color-coded. This listing includes baseline assessments in addition to post-treatment assessments. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Subject ID, Dose Number, Post Dose Day, Symptom.]

Treatment Group	Subject ID	Study Day	Abdominal Pain	Vomiting	Diarrhea	Allergic Reaction	Candidiasis
Placebo	SST.XXXX	1	MILD	MILD	NONE	SEVERE	NONE

16.2.7 Individual Laboratory Measurements

Listing 10: 16.2.7.1: Clinical Laboratory Results at Screening - Chemistry

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal results, e.g., 16.2 (Mild). The "extra" fields that are completed for abnormal results are not included in this listing; they are included in the listing of abnormal laboratory results that is included in the table shells document. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, and Planned Time Point.]

Treatment Group	Subject ID	Sex	Age (years)	Laboratory Parameter (Units)	Result

Listing 11: 16.2.7.2: Clinical Laboratory Results at Screening - Hematology

Treatment Group	Subject ID	Sex	Age (years)	Laboratory Parameter (Units)	Result

Listing 12: 16.2.7.3: PCT Levels

PCT Cohort	Treatment Group	Subject ID	Screening PCT Level (ng/mL)	D5V PCT Level (ng/mL)

16.2.8 Vital Signs and Physical Exam Findings

Listing 13: 16.2.8.1: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled. These listings are not color-coded, but the severity should be included in parentheses after the result for abnormal assessments, e.g., 100.7 (Mild). In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, Planned Time Point.]

PCT Cohort	Treatment Group	Subject ID	Planned Visit Day	Actual Study Day	Temperature (F)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse Rate (beats/min)	Respiratory Rate (breaths/min)	Oxygen Saturation (%)

Listing 14: 16.2.8.2: Physical Exam Findings

[Implementation Note: This listing includes all physical exam findings, scheduled and unscheduled. If a subject does not have any findings upon examination, they will not be included in this listing. If reported as an AE, display "Yes" with the AE Number in parentheses, e.g., "Yes (7)". In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification.] Sort order: PCT Cohort, Treatment Group, Subject ID, Planned Time Point.]

PCT Cohort	Treatment Group	Subject ID	Planned Visit Day	Actual Study Day	Body System	Abnormal Finding

16.2.9 Concomitant Medications

Listing 15: 16.2.9: Concomitant Medications

[Implementation Note: "Medication Start Day" and "Medication End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). For medication start dates that are > 30 days prior to enrollment, rather than use exact study days, categorize as follows:

- *5 years prior to enrollment*
- *1-5 years prior to enrollment*
- *1-12 months prior to enrollment*

If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Number in parentheses, e.g., "Yes (7)". In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Sort order: Treatment Group, Subject ID, and CM Number.]

PCT Cohort	Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for New or Worsening LRTI?

16.2.10 Clinical Improvement, Ordinal Clinical Outcome, Days of Antibiotics Use, DOOR, and Their Components

Listing 16: 16.2.10.1: Clinical Improvement, Ordinal Clinical Outcome, and DOOR

			D5V			D11V				D28V	
Subject ID	Treatment Group	Clinical Improvement	Ordinal Clinical Outcome	Days of Antibiotic Use	DOOR	Clinical Improvement	Ordinal Clinical Outcome	Days of Antibiotic Use	DOOR	Clinical Improvement	Days of Antibiotic Use
SST.XXXX	Placebo	Yes	3	2	60.5	Yes	1	6	20	Yes	10

Note: Observed values of Clinical improvement, ordinal clinical response, days of antibiotics use and DOOR are reported.

Listing 17: 16.2.10.2: LRTI Symptoms

Treatment Group	Subject ID	Study Day	Cough	Sputum Production	Chest Pain	Difficulty Breathing
Placebo	SST.XXXX	1	MILD	MILD	NONE	SEVERE

Listing 18: 16.2.10.3: Mortality Listing

Treatment Group	Subject ID	Date of Death	Death Related to Study Participation?	Death Associated with Persistent/Worsening LRTI?	Death Associated with UADE?	Death Associated with Hospitalization?	Comments
Azithromycin	SST.XXXX	01OCT2018	Yes or No	Yes/No	Yes/No: UADE #	Yes/ No: MAV #	

Listing 19: 16.2.10.4: Listing of Medically Attended Visits

[Implementation Note: Sort by PCT Cohort, Treatment Group, Subject ID, Date of Visit. If visit type is other, report as Other: Specify.]

PCT Cohort	Treatment Group	Subject ID	Date of Visit	Visit Type	Visit Associated with Persistent or Worsening LRTI	Non-Study Antibiotics Taken or Prescribed at this Visit?
	Azithromycin	SST.XXXX				

Listing 20: 16.2.10.5: Listing of Hospitalizations

[Implementation Note: Sort by PCT Cohort, Treatment Group, Subject ID, Date of Visit. If visit type is other, report as Other: Specify.]

PCT Cohort	Treatment Group	Subject ID	Date of Hospitalization	Cause of Hospitalization	Hospitalization Require Intensive Care Due to Persistent or Worsening LRTI?	Subject Die During Hospitalization?
	Azithromycin	SST.XXXX				

Listing 21: 16.2.10.6: Culture Results Listing

[Implementation Note: Sort by PCT Cohort, Treatment Group, Subject ID, Culture Site. For the Pathogens Identified Column, list all identified pathogens separated by a comma.]

PCT Cohort	Treatment Group	Subject ID	Culture Site	Collection Date	Collection Time	Culture Result	Gram-Positive Cocci Result[a]	Gram-Positive Rods Result[a]	Gram-Negative Cocci Result[a]	Gram-Negative Rods Result[a]	Pathogens Identified
	Azithromycin	SST.XXXX	Throat or Sputum or Blood,…	Yes or No	Yes/No	Positive or Negative					

[a] For negative blood culture results, 'Not Applicable' was used to report Gram stain results.

Listing 22: 16.2.10.6: Listing of Biofire Data from Nasopharyngeal Swabs

[Implementation Note: Sort by PCT Cohort, Treatment Group, Subject ID, Pathogen Type, and Pathogen.]

PCT Cohort	Treatment Group	Subject ID	Pathogen Type	Pathogen	Result
	Azithromycin	SST.XXXX	Virus	Influenza A	Detected
			Bacteria	Influenza A	Not Detected

APPENDIX 4. NCA TEMPLATE

Not applicable.