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 Number: 15-0020

DMID Funding Mechanism: Vaccine and Treatment Evaluation Unit

In Vitro Diagnostic Support Provided by: bioMérieux

Sponsor: NIH/NIAID/DMID

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ARLG Principal Investigator: Ebbing Lautenbach, MD, MPH, MSCE

DMID Clinical Project Manager: Marina Lee, PhD

Version Number: 6.0

28 February 2020

Statement of Compliance

This trial will be carried out in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 812);
- International Council on Harmonization (ICH) E6; 62 Federal Register 25691 (1997); and future revisions.
- The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule-Final Modification (45 CFR Parts 160 and 164);
- National Institutes of Health (NIH) Clinical Terms of Award, as applicable.

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator(s):

Signed: _____ Date: _____

Name
Title

Signed: _____ Date: _____

Name
Title

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LIST OF ABBREVIATIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
ARI	Acute Respiratory Infection
ARLG	Antibacterial Resistance Leadership Group
ATP	According-to-protocol
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMS	Clinical Materials Services
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOOR	Desirability Of Outcome Ranking
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IDES	Internet Data Entry System
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
JAMA	Journal of the American Medical Association
LRTI	Lower Respiratory Tract Infection
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
PCT	Procalcitonin
RADAR	Response Adjusted for Days of Antibiotic Risk
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
VAMC	Veterans Affairs Medical Center

Protocol Summary

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)

Phase: Not Applicable, IDE

Population: Approximately 560 evaluable, adult subjects, presenting as outpatients with suspected LRTI with a PCT level of ≤0.25 ng/mL. In order to achieve this number of evaluable subjects, up to 840 will be enrolled.

Number of Sites: 6

Study Duration: Approximately 36 months

Subject Participation Duration: Approximately 28 days

Description of Agent or Intervention: Diagnostic Device: VIDAS© 3 platform and VIDAS® B.R.A.H.M.S Procalcitonin (PCT) test

Study Drugs: Azithromycin and placebo

Objectives:

Primary:

- 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.

Secondary:

- To compare groups receiving azithromycin versus placebo with regard to all antibiotic use by Days 11 and 28.
- 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.
- To compare groups receiving azithromycin versus placebo with regard to emergency department visits by Days 11 and 28.

- 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.
- To compare groups receiving azithromycin versus placebo with regard to improvement in presenting symptoms by Days 11 and 28.
- 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.
- 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
- 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 "Response Adjusted for Days of Antibiotic Risk (RADAR)" methodology.
- To compare groups receiving azithromycin versus placebo in regard to solicited events by Day 5.
- 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 5.
- To compare groups receiving azithromycin versus placebo in regard to improvement in vital sign abnormalities or symptoms present at enrollment, on Day 5.
- 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.

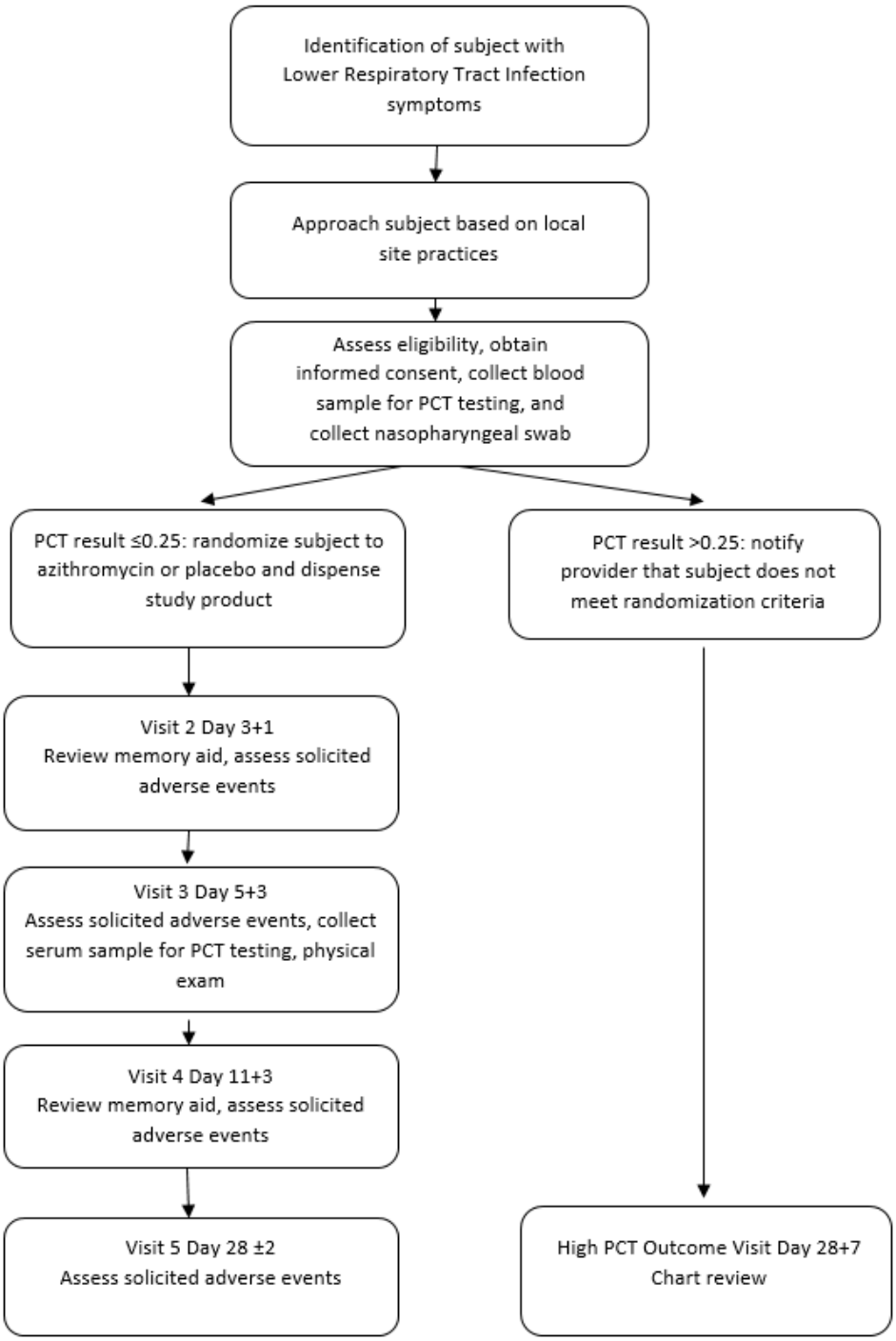
Exploratory:

- To compare PCT levels at Day 1 and Day 5 among treatment failures in the placebo and azithromycin groups
- 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 "Response Adjusted for Days of Antibiotic Risk (RADAR)" methodology
- To compare groups receiving azithromycin versus placebo in regard to solicited events by Day 11.
- 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.

- To compare groups receiving azithromycin versus placebo in regard to improvement in vital sign abnormalities or symptoms present at enrollment, on Day 11.
- 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.

Description of Study Design:	Double-Blind, Placebo-Controlled, Randomized, Non-Inferiority Trial
Estimated Time to Complete Enrollment:	36 months

Schematic of Study Design:



1 KEY ROLES

Lead Principal Investigator:	Ephraim L. Tsalik, MD, MHS, PhD Duke University
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Statistical and Data Coordinating Center:	The Emmes Corporation

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Inappropriate prescribing of antibacterials for viral acute respiratory infection (ARI) contributes to increased healthcare costs, unnecessary drug-related adverse effects, and is a major contributor to antimicrobial resistance (1-5). Oral antibiotics have been attributed to ~20% of Emergency Department (ED) visits for drug-related adverse effects, mostly due to allergic reactions (6). In addition, the Centers for Disease Control and Prevention (CDC) recently reported ~23,000 deaths annually in the US due to multidrug resistant organisms. Antimicrobial stewardship programs have proven effective in driving more appropriate antibiotic use in inpatient settings where tight control, mandatory education, and feedback are available. However, most inappropriate antimicrobial use occurs in patients with ARIs (7-9). These are among the reasons why developing improved diagnostics that can be applied in the outpatient setting has been recommended by numerous entities including the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

In the most general terms, infection represents a maladaptive interaction between pathogen and host that manifests in clinical disease. However, those outward manifestations (e.g., fever, cough, malaise) are non-specific. Identifying the cause of these non-specific symptoms has largely focused on pathogen identification. While important, this approach has limitations including issues related to low sensitivity, low specificity, inability to distinguish infection from colonization, sampling error, and delays between testing and results (10). Different pathogen identification strategies overcome some but not all of these limitations. As a complement to current pathogen-focused testing, host-based biomarkers can provide useful diagnostic information. This is predicated on the observation that patients respond differently to viral and bacterial infection. No biomarker has received more attention in this regard than procalcitonin (PCT).

PCT was first described in the setting of sepsis, where concentrations were increased compared to non-infectious conditions (11). Moreover, PCT has been used to distinguish bacterial from viral infection because interferon gamma production induced by viral infections inhibits PCT production (12). As a result, PCT-guided management of LRTI (including COPD exacerbation and pneumonia) has been used to withhold antibiotics or shorten the duration of antibiotic therapy without adversely affecting outcomes in several European studies (13-15). Specifically, low PCT values (≤0.25 ng/mL) were used to generate recommendations that antibacterials be withheld. Conversely, high PCT values prompted recommendations that antibacterials be provided. The results of these various studies are highlighted in a Cochrane database systematic review and showed that antibacterial use decreased by 50% without adversely affecting clinical outcomes (16).

This placebo-controlled, randomized, double blinded study represents an approach to the evaluation of PCT in LRTI that has not previously been evaluated. Based on the above evidence, we hypothesize that patients with suspected LRTI and a PCT value, ≤0.25ng/mL, are unlikely to have a bacterial infection, and hence, will not benefit from antibacterial therapy. Therefore, treatment of these patients with placebo will be non-inferior to antibacterial therapy.

2.2 Rationale

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.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

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 (16-19). 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, *Clostrdium difficile*-associated diarrhea, QT prolongation, and gastrointestinal upset (e.g., nausea, vomiting, diarrhea, or abdominal pain). Other treatment-related side effects occurred rarely (<1%).

2.3.2 Known Potential Benefits

If, as assessed by the primary outcome, placebo therapy is non-inferior to azithromycin, then not prescribing unnecessary antibiotics will reduce antibiotic exposure among adults with LRTI. The potential benefits of reduced antimicrobial exposure involve benefits both to the individual patient and the population as a whole.

Potential benefits to the individual patient include a lower risk of an adverse event associated with antibiotic therapy (e.g., antibiotic associated diarrhea, allergic reactions, drug-drug interactions, *Clostridium difficile* infection) and a lower risk of becoming colonized and subsequently infected with antibiotic-resistant bacteria.

Potential benefits to the population include a lower prevalence of colonization with pathogenic antibiotic-resistant bacteria among adults treated for LRTI. Since these antibiotic-resistant bacteria are transmissible, a lower prevalence of antibiotic-resistant bacterial colonization among the population treated for LRTI could decrease the risk of colonization by antibiotic-resistant bacteria among other persons in the population.

3 OBJECTIVES

3.1 Study Objectives

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.

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 "Response Adjusted for Days of Antibiotic Risk (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 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.

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 "Response Adjusted for Days of Antibiotic Risk (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 Study Outcome Measures

3.2.1 Primary Outcome Measures:

The efficacy of azithromycin versus placebo on Day 5 will be based on clinical improvement.

- Clinical improvement will be 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 (Table 1).
3. Absence of fever in the day preceding or at the Day 5 Visit (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) [18]

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. Clinical improvement will be 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 (Table 1).

- **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 Day 11 visit. 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 Day 11 Visit.

- **Note:** vital signs were not recorded at Days 11 and 28. Therefore, the subcomponents of clinical improvement at Day 11 and 28 are different from the subcomponents of clinical improvement used for the primary outcome measure at Day 5 (i.e., subcomponents at Day 11 and 28 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 (Table 1).
- 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.

7. The efficacy of azithromycin versus placebo on Day 28 will be based on clinical improvement. Clinical improvement will be 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 (Table 1).
- **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 Day 28 visit.
- **Note:** vital signs were not recorded at Days 11 and 28. Therefore, the subcomponents of clinical improvement at Day 11 and 28 are different from the subcomponents of clinical improvement used for the primary outcome measure at Day 5 (i.e., subcomponents at Day 11 and 28 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 (Table 1).
- 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).

8. Outcome assessed employing a superiority analysis using the “Response Adjusted for Days of Antibiotic Risk (RADAR)” approach.

  - The endpoint/outcome measure is the composite overall Desirability Of Outcome Ranking (DOOR) at Outcome Assessment on Day 5
  - DOOR is defined as follows:
    - Each subject is evaluated according to the ordinal clinical outcome (See Table 2 below)
    - DOOR is then assigned according to two rules:
      - When comparing two subjects with different ordinal clinical outcomes, the subject with a better clinical outcome receives a higher rank.
      - When comparing two subjects with the same ordinal clinical outcomes, the subject with fewer days of antibiotic use receives a higher rank.

Table 2. Ordinal Clinical Outcomes Assessed at Day 5

	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 3.2.1.
**Solicited events are defined in Table 3.

Table 3. Solicited Adverse Events for RADAR-DOOR ranking

	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

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. Response Adjusted for Days of Antibiotic Risk (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.

Table 4. Ordinal Clinical Outcomes Assessed at Day 11

	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 3.2.1 except temperature will be the only vital sign assessed at Day 11.

**Solicited events are defined in Table 3.

4 STUDY DESIGN

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, (see Eligibility criteria #1) 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. 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 measured from the time of the first dose of study drug through approximately Day 28. Efficacy outcome assessments include assessment of presenting signs and symptoms, vital signs, antibiotic usage, return visits to a physician's office, emergency department 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, emergency department visits, urgent care, and hospitalizations. Chart review will also identify whether antimicrobials were prescribed at the enrollment visit or subsequent visits through 28 days. 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 Appendix A, Schedule of Events). Additional informed consent will be obtained for future use sample collection.

Details on study procedures and evaluations and study schedule are included in Sections 7 and 8 and Appendix A Schedule of Events.

The primary outcome measure is the non-inferiority of placebo versus azithromycin on Day 5 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.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study will recruit potential subjects 18 years of age or older who are suspected to have LRTI. In order to meet the primary objective, the study requires 560 evaluable subjects (approximately 280 per group). Taking into account subjects who withdraw, fail to complete Visit 3, or do not meet other inclusion criteria for the ATP population at Day 5 as defined in Section 11.4, this study will randomize approximately 674 enrolled subjects (approximately 337 per group) with PCT ≤0.25. ng/milk 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), New York (University of Rochester) and Texas (Houston VA Medical Center).

Clinical research personnel will approach patients meeting the clinical criteria (see inclusion criteria below) to discuss the study with them. Those who agree to participate will be consented for study enrollment and for future use samples. Declination to participate in collection of future use samples will not affect participation in the primary study. All enrolled subjects will have samples obtained including blood for PCT measurements and nasopharyngeal swabs for etiology testing. Subjects with a PCT ≤0.25 ng/mL will be randomized 1:1 to receive oral azithromycin or placebo.

Subjects with a PCT >0.25 ng/mL will not be randomized and will not receive study treatment. These subjects will have their charts reviewed for roughly 28 days after enrollment. Providers will be notified that the patient will not be randomized and therefore, the treating provider should make treatment decisions.

This type of consenting ensures that only patients who are willing to proceed to randomization and subsequent study activities are screened for PCT levels. Potential subjects will be identified at any time following clinical diagnosis of LRTI. Other forms and/or mechanisms of recruitment may also be used. The local IRB will approve recruitment materials prior to use.

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.

5.1 Subject Inclusion Criteria

Subjects must meet all of the inclusion criteria to be enrolled in this study.

1. Clinician suspected LRTI[1] based on the presence of at least two qualifying symptoms[2] OR one qualifying symptom and at least one qualifying vital sign.[3]

[1] *LRTI will include acute bronchitis, tracheitis, tracheobronchitis, asthma exacerbation, and acute exacerbation of COPD but does not include known pneumonia.*

[2] *New cough, worsening of chronic cough, new sputum production, increased volume or purulence of chronic sputum production, chest pain, and difficulty breathing*

[3] *Fever (Provider or patient-measured temperature ≥37.8°C (100.0°F) or patient-reported feverishness), tachycardia of ≥90 beats/minute, tachypnea of >20 breaths/minute*

2. Males and females age ≥18 years old.
3. Presentation ≥24 hours and ≤ 28 days after the onset of at least one qualifying symptom related to the acute episode of illness.
4. Ability to understand study procedures and willing and able to comply with all required procedures and visits for the entire length of study.
5. Provide written informed consent before initiation of any study procedures.

5.2 Subject Exclusion Criteria

All subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Hospitalized prior to screening and enrollment. Subjects enrolled in clinic or ED setting and then hospitalized during the same clinical encounter may be included.
2. Chronic pulmonary conditions at the investigator's discretion[4]

   [4] *Such as:*

   - *Noninvasive ventilation use for any indication other than obstructive sleep apnea*
   - *Long-term invasive mechanical ventilation for any indication*
   - *Known diagnosis of cystic fibrosis or chronic bronchiectasis.*

3. Receipt of an investigational product within 30 days prior to Day 1 or plans to potentially start any investigational product within 30 days after the subject's anticipated study completion.
4. Current enrollment in another clinical trial of an investigational agent
5. Known or suspected infection at any other anatomic site requiring antibacterial therapy.
6. Immunosuppression.[5]

   [5] *Includes:*

   - *HIV infection with CD4<200 based on last known measurement or patient-reported value*
   - *History of hematologic malignancies*

- *Receipt of chemotherapy within the previous 6 months or anticipated receipt of chemotherapy during the study period (1 month)*
- *Known to have an absolute neutrophil count of <500 cells/mL or an expectation of an absolute neutrophil count of <500 cells/mL during course of the study,*
- *Current systemic corticosteroid use (equivalent of 20mg prednisone per day for ≥2 weeks within the last month)*
- *Systemic non-steroid immunosuppressive or biologic therapy for transplant, rheumatologic conditions, or other conditions within the last month. Biologics used specifically for control of moderate to severe asthma, including anti-IgE monoclonal antibody therapy (Xolair) or IL-5 monoclonal antibodies (Mepolizumab and Reslizumab) are allowed.*

7. Contraindication to the use of azithromycin including history of allergy or intolerance to azithromycin or known prolonged QTc interval (>500msec).

8. Any condition that in the judgment of the referring provider or site investigator precludes participation because it could affect subject safety or ability of subject to participate in this trial.

9. Prior use of azithromycin in the past two weeks.

10. Use of any systemic antibiotic in the previous 24 hours.

11. Previous randomization in this trial.

5.3 Subject Randomization Criteria

Once enrolled, to be eligible for randomization subjects also must have PCT ≤0.25 ng/mL.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

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 The Emmes Corporation's 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.

5.4.2 Masking Procedures

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.

5.4.3 Reasons for Withdrawal and Discontinuation of Treatment

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.

If a subject experiences any individual halting rule, as defined in Section 9.5.2, they will discontinue treatment with the study drug but will not be withdrawn from the study.

5.4.4 Handling of Withdrawals and Discontinuation of Treatment

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Subjects will be encouraged to complete an Early Termination Visit. Although subjects are free to withdraw at any time or may be withdrawn by the site principal investigator or appropriate sub-investigator at any time, subjects who receive at least one dose of study product will be encouraged to remain in the study for follow-up safety assessments.

Every attempt will be made to follow all protocol defined safety follow-up (solicited adverse events) to resolution or stabilization.

Subjects who withdraw, or are withdrawn or terminated from the study, or discontinue treatment will not be replaced.

5.4.5 Termination of Study

The National Institute of Allergy and Infectious Diseases (NIAID), or each site's IRB of record may discontinue the study at any time. Should the study be discontinued prior to completion, any subjects on study will complete study visits, if medically appropriate, but no new subjects will be enrolled.

Although the study Sponsor has every intention of completing this study, it reserves the right to terminate this study at any time for clinical or administrative reasons. Reasons for termination include, but are not limited to, study closure due to DSMB review and recommendation and at the discretion of DMID.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

Azithromycin

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 $C_{38}H_{72}N_2O_{12}\bullet 2H_2O$ and a molecular weight of 785.0.

VIDAS® B.R.A.H.M.S Procacitonin Test

The VIDAS® B.R.A.H.M.S PCT is an automated test for use on the VIDAS instruments for the determination of human procalcitonin in human serum or plasma using the Enzyme-Linked Fluorescent Assay (ELFA) technique. The VIDAS® B.R.A.H.M.S PCT is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock. It is also used in conjunction with other laboratory findings and clinical assessments to aid in decision making on antibiotic therapy for patients with suspected or confirmed LRTI, or patients with suspected or confirmed sepsis.

6.1.1 Acquisition

6.1.1.1 Azithromycin and Placebo

Over-encapsulation, packaging, and labeling of study drug will be performed according to applicable regulatory requirements. All study drugs (azithromycin and placebo) will be distributed through the DMID Clinical Materials Services (CMS, Fisher BioServices).

Study product (azithromycin and matching placebo) will be shipped from the DMID CMS to the study sites upon request and approval by DMID.

6.1.1.2 VIDAS® B.R.A.H.M.S Procalcitonin Research Test Kits

The VIDAS® B.R.A.H.M.S PCT Kits for the trial will be provided by bioMerieux and distributed through the DMID Clinical Materials Services (CMS). The kits will be manufactured following current good manufacturing practices (cGMP) and labeled as investigational use only (IUO). The kits will be shipped to CMS under controlled condition defined by the package insert (also refer as IFU) with tracking documents. CMS will be responsible for maintaining the kits under proper condition, distributing the kits to the testing labs, and controlling the inventory and accountability after receiving products from bioMerieux. The VIDAS® B.R.A.H.M.S PCT will be shipped from the DMID CMS to the study sites upon request and approval by DMID.

6.1.1.3 VIDAS® 3 Platform Research Lab

The VIDAS® 3 platform will be provided, installed and qualified by field service engineers (FSE) from bioMerieux prior to initiation of the clinical evaluation. The participating laboratory sites will be CLIA-certified laboratories (or equivalent) capable of performing VIDAS® B.R.A.H.M.S PCT testing on VIDAS®3 platform and reporting the results to clinical sites within turnaround time defined in this trial.

Annual maintenance will also be provided by bioMerieux. The general maintenance will be performed by the testing laboratory per the user's manual. After the completion of the trial, the instruments will be deinstalled by bioMerieux FSE and shipped back to bioMerieux

6.1.1.4 VIDAS® B.R.A.H.M.S Procalcitonin Clinical Test Kits

With prior approval of DMID, CLIA certified clinical laboratory services for VIDAS® B.R.H.A.M.S. procalcitonin measurement may be used. Test kits will be obtained through routine clinical laboratory procedures. Results will be reported to the study team within the protocol specified time frame.

6.1.2 Formulation, Packaging, and Labeling

6.1.2.1 Azithromycin and Placebo

Azithromycin will be supplied as 250 mg over encapsulated tablets. Each capsule will contain one-250mg azithromycin tablet and an inert filler.

Placebo will be supplied as matching capsules containing an inert filler. In order to maintain the blind, the capsules are the same size, weight, and color as the capsules containing Azithromycin tablets.

Additional details will be provided in the protocol-specific MOP.

All study products will be packaged in identical containers each containing 6 capsules. Each container will also be labeled in compliance with applicable regulatory requirement, including the FDA- required cautionary statement *"Caution-New drug-Limited by Federal (or United States) Law to Investigational Use Only."*

6.1.2.2 VIDAS® B.R.A.H.M.S Procalcitonin Test Kits

The VIDAS® B.R.A.H.M.S. PCT kit consists of 60 tests. The contents of the kit are 60 PCT strips (each strip consists of 10 wells), 60 ready to use solid phase receptacles (SPR) coated with mouse monoclonal anti-human procalcitonin immunoglobulins, 2 lyophilized PCT controls C1 and C2, 2 lyophilized PCT calibrators S1 and S2 and a master lot entry card (MLE).

6.1.3 Product Storage and Stability

6.1.3.1 Azithromycin and Placebo

Azithromycin and placebo capsules must be stored at 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F and 86°F) are permitted. [See USP Controlled Room Temperature].

6.1.3.2 VIDAS® B.R.A.H.M.S Procalcitonin Test Kits

The VIDAS® B.R.A.H.M.S. PCT kit must be stored at 2°C to 8°C (35° to 46°F). DO NOT Freeze reagents, with the exception of calibrators and controls after reconstitution. All unused reagents must be stored at 2°C to 8°C (35° to 46°F). Additional information and details can be found in the package insert.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

6.2.1 Azithromycin and Placebo

Azithromycin 500 mg or placebo (administered orally as two 250 mg capsules or two matching placebo capsules) as a single dose within 24 hours of randomization, 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.

6.3 Modification of Study Intervention/Investigational Product for a Subject

No modifications of study product are planned at this time. If a subject experiences any individual halting rule, as defined in Section 9.5.2, they will be taken off of the study drug.

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

6.4.1 Azithromycin and Placebo

After receipt of the study product, the site Principal Investigator (PI) is responsible for distribution and disposition of these study products, and has ultimate responsibility for drug accountability. As this is a blinded study, the site PI will delegate this responsibility to the unblinded site pharmacist. Study product records must be maintained and document logs of receipt, accountability, and storage temperature conditions. These study product accountability and dispensing logs must be maintained in the study file. Upon completion of the study and after the final monitoring visit, unused study product that has not been dispensed will be retained until monitored and released for disposition as per the Sponsor.

6.4.2 VIDAS® B.R.A.H.M.S. Procalcitonin Test Kits

After receipt of the VIDAS PCT kits, the site PI is responsible for distribution and disposition of these kits, and has the ultimate responsibility for PCT kits accountability. The site PI will delegate this responsibility to the site CLIA certified laboratory personnel.

VIDAS PCT kits must be maintained and document logs of receipt, accountability, and storage temperature conditions. These kit accountability logs must be maintained in the study file. Upon completion of the study and after the final monitoring visit, unused kits will be retained until monitored and released for disposition as per the Sponsor.

When a clinical laboratory performs procalcitonin testing, standard operating procedures as defined by CLIA guidelines will be used to document the receipt, accountability, and storage of PCT kits.

6.4.3 VIDAS® Platform

The normal maintenance of the VIDAS® platform will be performed and documented by the laboratory. Annual maintenance of the VIDAS® 3 instruments will be provided by bioMerieux. For sites where PCT is measured in a CLIA-certified clinical laboratory, maintenance will be performed according to standard operating procedures as defined by CLIA.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

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 Study Visit 3. 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.

6.6 Concomitant Medications/Treatments

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. Any symptomatic treatment received on the day of/during the enrollment visit will not be recorded unless it is a non-study systemic antibiotic.

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 (see Section 5.2). 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.

7 STUDY SCHEDULE

7.1 Screening

Each study site will determine the most efficient procedures to identify potentially eligible subjects from primary care clinics, urgent care centers, and emergency departments (EDs) affiliated with the study clinical trial centers. Providers will be informed about the study and provided with a TRAP-LRTI information pamphlet summarizing the study design and subject eligibility criteria. Providers may also be asked to alert their patients about their practice's participation in the TRAP-LRTI study, instructing them that study personnel may contact them to discuss potential research opportunities.

The identification of potentially eligible subjects will vary by site and practice setting and will include direct communication with providers, review of clinical intake logs, and electronic health record (EHR) alerts that automatically screen for LRTI cases from medical records.

Suspected LRTI will be defined as specified in eligibility criteria #1.

Once a potentially eligible subject with suspected LRTI is identified, study staff will coordinate with clinical providers based on local site practice. Study staff will then approach the eligible subject to explain the study protocol and describe the inclusion/exclusion criteria.

7.2 Enrollment/Baseline- Visit 1 (Day 1)

At the Enrollment Visit, study staff will obtain written informed consent from the subject for the primary study and for future use of samples and data. Declination to participate in collection of future use samples will not affect participation in the primary study. After the subject has had the opportunity to ask questions and has signed the informed consent document, the following activities will be performed:

- Eligibility criteria for enrollment will be reviewed;
- An assessment of LRTI signs and symptoms will be made
- Blood samples will be obtained and used for PCT measurement and future use (if consented).

Additional information will be obtained from the subject as follows:

- A complete medical history and sociodemographic data will be obtained by direct interview of the subject and medical record review
- A physical examination will be performed to determine general appearance and focused HEENT, neck, cardiopulmonary, and abdominal examinations; vital signs, including

temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry (obtained clinically).

** Note: physical examinations may be performed by physicians, advanced practice nurses, physician assistants, or nurses obtained either by study investigators or as part of clinical care.*

- Concomitant medications taken in the last 30 days will be recorded based on subject report or medical record review (see section 6.6. for details)

- A nasopharyngeal swab specimen will be collected for respiratory viral testing and banking.

The PCT value is expected to be available to the investigator within 2 hours of the blood draw. The study team will not report PCT results to the subject or the provider. Once the subject's PCT value is available, subjects with a PCT > 0.25 ng/mL will not be randomized. Providers will be notified that the patient will not be randomized and therefore, the treating provider should make treatment decisions.

Subjects with PCT ≤ 0.25 ng/mL will be randomized 1:1 to receive oral azithromycin or placebo and the following procedures will be performed:

- Study product will be dispensed and study staff will review the study product with the subject and review the study product storage and dosing instructions. Preferably, the study staff will witness the subject take the first dose of study product, which will be recorded on the memory aid.

- Subjects will be provided with a memory aid and other study-related materials to record daily temperature, solicited events, specified symptoms, concomitant medications, daily dose administration, and any unscheduled medical visits. Study staff will instruct the subject to complete the memory aid in order to assess adherence and to bring the aid and the medication bottle with them to Visit 3. Study staff will also train subjects on proper completion of the memory aid used to assess specific, solicited events.

7.3 Follow-up Visits for Randomized Subjects

7.3.1 Visit 2 (Day 3 + 1 day)

Study subjects will be evaluated on Day 3 via telephone. During the telephone call, study personnel will assess LRTI signs and symptoms. If the study team identifies concerns about worsening of clinical status, the subject will be advised to seek care from his/her provider or the nearest ER if indicated. Study staff will assist in facilitating the follow up appointment. This includes signs or symptoms of pneumonia (including fever, increased difficulty breathing, or increased/worsening cough) or development of a severe solicited event. The study staff will also review any new or changed concomitant medications with the subject. UADEs will be recorded if any occur.

Study staff will also ask about medication compliance and any solicited adverse events.

7.3.2 Visit 3 (Day 5 + 3 days)

The visit on Day 5 will represent the primary outcome assessment and will include an assessment of LRTI signs and symptoms. Also at Day 5, blood samples will be collected for repeat PCT testing. To permit evaluation of the secondary RADAR outcomes, all clinical parameters pertinent to the RADAR assessment will be ascertained at this time. This will be an in-person visit conducted at the study site. This visit can also be conducted in the subject's home.

Prior to this visit, study staff will make a preliminary assessment of the clinical response using the electronic health record to determine whether any of the following events have occurred after randomization and anticipated receipt of at least one dose of study agent.

- The subject had a medically attended visit to an ED, urgent care, or clinic;
- The subject was hospitalized during a separate clinical encounter following the enrollment encounter
- The subject received non-study, systemic antibiotic therapy

At the Day 5 visit, study staff will complete the following procedures:

- Assessment of clinical improvement including:
    - Review and collection of vital signs
    - Assessment and grading of LRTI symptoms
    - Occurrence of any medically attended visits
    - Receipt of any non-study systemic antibiotics
- Abbreviated physical examination to include general appearance and focused HEENT, neck, cardiopulmonary, and abdominal examinations;
- Review of the subject's memory aid
- Assess and record any solicited events and UADEs
- Review of memory aid and study product bottle (if available) to assess treatment compliance
- Obtain blood sample for PCT testing
- Review of study product bottle for drug accountability, if available;

If the subject develops signs or symptoms of pneumonia (including fever, increased work of breathing, increased/worsening cough, or new pulse oximetry reading ≤90%) or develops a severe solicited event, the subject will be referred to his/her primary care provider or local urgent care center/ED. Study staff will assist in facilitating the follow up appointment. The study

staff will share all pertinent information related to the study with the treating clinician including treatment arm assignment if clinically indicated as determined by the treating clinician and the study's site investigator.

7.3.3 Visit #4 (Day 11 + 3 days)

Study subjects will be evaluated on Day 11 via telephone. Secondary and exploratory outcome measures will be assessed at this follow up. Study staff will complete the following procedures:

- Assessment of clinical improvement including:
    - Review and collection of temperature
    - Assessment and grading of LRTI symptoms
    - Occurrence of any medically attended visits
    - Receipt of any non-study systemic antibiotics
- Review of the subject's memory aid
- Assess and record any solicited events and UADEs

If the subject develops signs or symptoms of pneumonia (including fever, increased work of breathing, or increased/worsening cough) or develops a severe solicited event, the subject will be referred to his/her primary care provider or local urgent care center/ED. Study staff will assist in facilitating the follow up appointment. The study staff will share all pertinent information related to the study with the treating clinician including treatment arm assignment if clinically indicated as determined by the treating clinician and the study's site investigator.

7.3.4 Visit # 5 Final Visit (Day 28 ± 2 days)

Study subjects will be evaluated on Day 28 via telephone. Secondary outcome measures will be assessed at this follow up. Study staff will complete the following procedures:

- Assessment of clinical improvement including:
    - Review and collection of temperature
    - Assessment and grading of LRTI symptoms
    - Occurrence of any medically attended visits
    - Receipt of any non-study systemic antibiotics
- Assess and record any UADEs

If the subject develops signs or symptoms of pneumonia (including fever, increased work of breathing, or increased/worsening cough) or develops a severe solicited event, the subject will be referred to his/her primary care provider or local urgent care center/ED. Study staff will assist in facilitating the follow up appointment. The study staff will share all pertinent information

related to the study with the treating clinician including treatment arm assignment if clinically indicated as determined by the treating clinician and the study's site investigator.

The study staff will also review any new or changed con-commitment medications with the subject. A review of the medical record will also be done to recording results of clinical laboratory evaluations as specified in Section 8.2.1.

The exact date of the follow-up visit will be documented throughout the study.

7.3.5 Early Termination Visit

Subjects who are withdrawn from the study will be asked to complete an early termination visit. Procedures at the early termination visit will be identical to the next scheduled visit for outcome assessment. Subjects who withdraw from the study will be asked if they agree to receive a follow-up phone call approximately one week after their withdrawal, which will constitute the early termination visit. If the subject agrees, study staff will determine if any follow-up medical care was sought, any solicited adverse events occurred or if there was any change in medical history.

If the subject presents to the Early Termination visit with symptoms concerning for active illness in need of medical attention, such as fever and/or elevated respiratory rate, the study team will refer the subject to seek care and to follow up with their primary care provider.

UADEs will be recorded if any occur.

7.3.6 Unscheduled Visit

N/A

7.4 Follow-up for Non-randomized Subjects

7.4.1 Visit #5N (Day 28+7)

At enrollment, subjects with a PCT level > 0.25 ng/ml will still have data and samples collected but they will not be randomized. Their charts will be reviewed through 28 days after enrollment in order to support future use research. This may include recording the results of clinical laboratory evaluations as specified in Section 8.2.1. Review of medical history will be performed to determine whether medically attended visits or receipt of systemic antibiotics have occurred.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

A medical history will be obtained by direct interview during the screening process. Potential subjects will be queried regarding a history of significant comorbidities, current medications, and allergies including drug allergies. Medication history (concomitant medications) will include a review of all medications taken in the last 30 days (see section 6.6. for details). Use of non-study systemic antibiotics will be reviewed at each visit following enrollment. Concomitant medications will be reported in the eCRF. Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. Use of new medication should prompt evaluation for the presence of a new diagnosis of an acute or chronic medical disease or condition. At follow-up visits, an interim medical history will be obtained by interview of subjects noting any changes since the previous clinic visit or contact. The interim medical history should include an assessment for new medical conditions.

At the enrollment visit (Day 1), a clinical assessment to assess eligibility will occur, which will include vital signs (temperature, blood pressure, pulse, respiratory rate, and pulse oximetry). If indicated based on subject's medical history or medical/nursing assessment, a physical examination, conducted as part of the clinical care or by a study clinician licensed to make medical diagnoses*, will occur. This could include a focused HEENT, neck, cardiopulmonary, and abdominal examinations.

An assessment of clinical improvement will occur at each follow-up visit. The assessment will include documentation of maximum temperature in the preceding 24 hours; normalization of respiratory rate (at the in-person visit); presence and extent of cough, sputum production, chest pain, and difficulty breathing; occurrence of medically attended visits including visits to the emergency department (ED), primary care physician, study physician, and urgent care; hospitalizations; and use of non-study systemic antibiotics (parenteral or oral). Vital signs (temperature, blood pressure, pulse, pulse oximetry, and respiratory rates) will be collected at the enrollment visit and at each in-person follow-up visit.

Solicited event assessments will include an assessment of solicited events occurring from the time of enrollment through Visit 4 (Day 11+3 days). All subjects will be instructed to complete a subject memory aid from the time of enrollment through Visit 4 (Day 11+3 days). Subject memory aids will be reviewed with the subject for any discrepancies or missing data and data will be recorded by study coordinators.

** Note: physical examinations may be performed by physicians, advanced practice nurses, physician assistants, or nurses.*

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

No clinical safety laboratory studies will be performed as part of this protocol.

To further describe the enrolled population, we will document the following from existing site medical records and laboratory results:

- White blood cell count and differential including site-specific normal ranges,
- Results of blood or respiratory tract cultures, antigen tests, or molecular assays, and
- *Streptococcal pneumoniae* or *Legionella pneumophila* serotype 1 urinary antigen testing.

8.2.2 Special Assays or Procedures

N/A

8.2.3 Specimen Preparation, Handling and Shipping

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

At the time of enrollment, a serum or plasma sample and nasopharyngeal sample will be collected. If the subject consented for future use, then PAXgene Blood RNA will also be collected. Another serum or plasma sample will be obtained at the Day 5 visit.

Nasopharyngeal specimens will be collected using flocked swabs. These swabs will be placed in universal transport medium. See the MOP for detailed instructions on processing and storage of these samples.

If the subject consented for future use, the PAXgene tubes should be inverted 8-10 times and stored upright at room temperature for a minimum of two hours prior to processing. Refer to the MOP for detailed instructions on processing and storage of these samples.

The sample collection, preparation, and testing must follow the VIDAS B.R.A.H.M.S Procalcitonin (PCT) package insert, also referred to as Instruction for Use (IFU). Additional details are described in the MOP. For this protocol it is preferred that a green-top lithium heparin tube is used for the collection of plasma but a red-top serum separator tube is also allowable.

Note: *Blood sampling tube results may vary from one manufacturer to another depending on the materials and additives use. It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.*

It is recommended not to use samples which appear to be hemolyzed, lipemic, or icteric and, if possible, to collect a new sample.

Samples collected in EDTA tubes cannot be used for PCT testing in this trial.

Specific instructions are included in the Manual of Procedures (MOP).

8.2.3.2 Specimen Shipment

Nasopharyngeal swabs and serum/plasma samples will be shipped on dry ice to the DMID CMS in batches using only IATA-approved Category B shipping boxes. All packages will be labeled and documented correctly per current regulations, and a detailed manifest will be included. Packages will be shipped priority overnight, tracked en route, and delivery will be confirmed to ensure the package arrived in good condition. A specimen tracking log will be completed for every shipment.

Specific instructions will be included in the Manual of Procedures (MOP).

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

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 only solicited adverse events will be collected.

Additionally, a blood draw is minimum risk since there is no more risk than the normal standard of care.

The collection of the nasopharyngeal swabs is minimum risk with some discomfort possibly experienced by the subject; in some cases, it may cause mild bleeding. This risk is no greater than encountered during the collection of such swabs for routine clinical care.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Adverse Event (AE): International Council on Harmonisation (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

9.2.2 Solicited Adverse Events

Solicited adverse events are common and known to occur following administration of the study product. Solicited adverse events will be recorded according to the study timeline. Solicited adverse events will be used to determine DOOR assignment as summarized in Table 3, Section 3.

9.2.3 UADE Definition

An unanticipated adverse device effect (UADE) per 21 CFR 812.3(s): is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a

supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.3 Reporting Procedures

9.3.1 Reporting UADEs Using SAE Forms

Unanticipated adverse device effect (UADE) are unexpected and will be reported appropriately should any occur. Any UADE must be entered into AdvantageEDC℠ (within 24 hours of site awareness) and reported to the IRB. Please see the protocol-specific MOP for details regarding this procedure.

9.3.2 Reporting for Studies Conducted Under DMID Sponsorship

Any UADEs will be collected from the first study enrollment through study completion. The Site Investigator is responsible for documenting and reporting all UADEs that are reported during the study, regardless of their relationship to study procedures.

Information to be collected includes a record of any concomitant medication, event description, time of onset, clinician's assessment of severity and relationship to study procedures/study device. All UADEs will be followed to adequate resolution or stabilization. Resolution of an UADE is defined as the return to pre-enrollment status or stabilization of the condition with the expectation that it will remain chronic. Time of resolution/stabilization of the event will be collected for device procedure related UADEs.

DMID will evaluate each report of a UADE in accordance with 21CFR812.46(b). DMID will notify the FDA, all participating site principal investigators (i.e., all principal investigators to whom the sponsor is providing study device), and all reviewing IRBs through the participating sites' principal investigators. Notification will occur as soon as possible but in no case later than 10 working days after the sponsor is notified of the UADE. Relevant follow up information to a safety report will be provided as soon as the information is available.

9.3.3. Reporting of Pregnancy

The only active treatment in this study is azithromycin, which is a pregnancy Class B drug. It is used as a standard treatment in pregnant women. As such, pregnancy will neither be screened for nor reported but may be collected per medical history.

9.4 Type and Duration of the Follow-up of Subjects After Adverse Events

Study related solicited events and UADEs will be followed until resolved or considered stable.

9.5 Halting Rules

9.5.1 Study Halting Rules

Subject safety data will be reviewed on an ongoing basis. If any of the following events occur while a subject is on study, then enrollment will be stopped, and data will be reviewed. A decision to proceed or to terminate the trial will be made in consultation with the DSMB (including the independent safety monitor), NIH/NIAID/DMID, and the clinical investigators.

Further study enrollment will be halted for DSMB review/recommendation if any of the following are reported:

- Hospitalization of 5 subjects (or ≥5% if more than 100 subjects randomized) that requires intensive care due to persistent/worsening LRTI within 28 days of initiation of study treatment
- More than 10 subjects (≥10% if more than 100 subjects randomized) require hospitalization for persistent/worsening LRTI within 3 days of initiation of study treatment
- More than 20 subjects (≥20% if more than 100 subjects randomized) require the administration of non-study directed systemic antibiotic therapy for persistent/worsening LRTI within 3 days of initiation of study treatment
- Any subject experiences death (that is not the result of trauma or accident) prior to Visit 4 (Day 11+3 days) **and** that is suspected to be related to study treatment (or participation).

9.5.2 Individual Halting Rules (Termination of Study Product Administration)

Study product administration may be discontinued if any of the following criteria are met:

- Any clinical adverse event (AE), intercurrent illness, or other medical condition occurs that, in the opinion of the investigator, continued receipt of study product would not be in the best interest of the subject;
- New onset of illness or condition that meets exclusion criteria, at the investigator's discretion
- Inadequate clinical response that requires off-study antimicrobial therapy.
    - Subjects who require off-study antimicrobial therapy will be defined as having an inadequate clinical response.

Subjects may stop study drug treatment at any time of their own volition or at the advice of their treating provider or the study investigators. Subjects who stop study product for any reason will be regarded as having withdrawn from treatment but not as having withdrawn from the study (i.e, subjects will be asked to continue to participate in follow-up visits). All subjects with an inadequate clinical response will be referred to a non-study healthcare provider for evaluation and possible treatment outside of the clinical study. If requested, unblinding can occur if clinically indicated as determined by the treating clinician and the study's site investigator.

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.

9.6 Safety Oversight

9.6.1 Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to the study. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial.

The DSMB will review study progress and subject, clinical and safety data at the following time points:

- Annually at the completion of each respiratory disease season;
- Final review meeting, approximately 6-8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for this trial. The data will be provided in a standard summary format;
- Ad hoc when a halting rule is met, for immediate concerns regarding observations during the study, or as needed.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews/meetings will be defined in the charter. The DSMB will review applicable data to include, but not limited to, study progress and subject, clinical, and safety data that may include enrollment and demographic information, medical history, concomitant medications, physical examination, dosing, and solicited events. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by group. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during the study as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate the study.

DMID, the PI, or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of the study. The DMID Medical Monitor is empowered to stop enrollment and study treatment if the halting criteria is met or in case of any safety concern.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that the study is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID in a separate monitoring plan and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to the study site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site principal investigators to discuss visit findings.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypothesis

The primary hypothesis is that placebo therapy is non-inferior in efficacy to azithromicyn treatment in terms of clinical improvement rates when administered to adults with suspect lower respiratory tract infection (LRTI) and a procalcitonin level of ≤0.25 ng/mL. The primary time point of interest is 4 days after administration of study product (i.e. Day 5).

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.

11.2 Sample Size Considerations:

The study will be powered to the primary endpoint of clinical improvement with 560 participants included in the according-to-protocol analysis population at Day 5. To achieve this sample size, approximately 674 enrolled subjects will need to be randomized (1:1) to placebo or azithromycin treatment to 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 57.6% in each group using a two-sided 95% confidence interval with continuity correction, in a per-protocol analysis (i.e., allowing for 16.9% loss in each treatment group to follow up/rescue medication).

The primary analysis will include an intention-to-treat (ITT) estimation of the difference in proportions of subjects with clinical improvement at Day 5 in the antibiotic and placebo groups with a two-sided 95% confidence interval.

11.3 Planned Interim Analyses

11.3.1 Safety Review

An interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical examination, dosing compliance, and solicited adverse events. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. The DSMB will meet and

review this data at scheduled time points or ad hoc as needed during this trial as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with the study treatments, and to continue, modify, or terminate this trial.

Additionally, this trial will be monitored to determine if any of the study halting rules described in Section 9.5.1 are met.

11.3.2 Interim Analysis of Efficacy, Futility, and Safety

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 ≤0.25 ng/mL

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. Original assumptions were that the overall rate of clinical improvement at Visit 3 would be 80% and there would be no more than 15% unevaluable subjects (i.e. withdraw, fail to complete Visit 3 or didn't meet other inclusion criteria for the according-to-protocol population at Day 5, as defined in Section 11.4) 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 a per-protocol analysis at Day 5. Due to findings at the interim analysis, 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.

11.4 Final Analysis Plan

The intention-to-treat (ITT) analysis population will consist of all randomized subjects. According-to-protocol (ATP) analysis populations will consist of subjects with no major protocol deviations regarding inclusion/exclusion criteria that consumed 5 doses of study product by Visit 3. The first dose of study drug should be taken within 24 hours of randomization. Subjects who miss a scheduled dose but resume the recommended dosing schedule within 24 hours remain eligible for ATP. However, in order for a subject to be eligible for the ATP-5 analysis, Visit 3 should be performed on or after the last day of study drug consumption while remaining within the 5+3 window. The ATP-5 analysis population will have the further restriction that the subjects must have completed an in-person Visit 3 within the protocol-defined time window. The ATP-11 analysis population will consist of the ATP analysis population with the further restriction that the subjects must have completed Visit 4 within the protocol-defined time window. The ATP-28

analysis population will consist of the ATP analysis population with the further restriction that the subjects must have completed Visit 5 within the protocol-defined time window.

Unless otherwise stated, all hypothesis tests and confidence intervals will be two-sided with α=0.05. Statistical tests and confidence intervals will not correct for multiplicity.

11.4.1 Primary Analysis

The non-inferiority of placebo versus azithromycin with respect to clinical improvement on at Visit 3 (as defined in Section 3.2.1), using a non-inferiority margin of 12.5%, will be determined for the ITT analysis population using a 95% confidence interval of the difference in proportions of clinical improvement as constructed using multiple imputation of clinical improvement with linear regression. The study Day that Visit 3 occurred on will be included as a covariate. A lower bound of the confidence interval greater than -12.5% will result in the conclusion of non-inferiority of placebo. At minimum, the imputation model will utilize available information collected at baseline and any completed study visits. Further details of the imputation model will be described in the SAP.

11.4.2 Secondary Analyses

1. The non-inferiority analysis of placebo versus azithromycin with respect to clinical improvement at Visit 3 (as defined in Section 3.2.1), using a non-inferiority margin of 12.5%, will be repeated as described in Section 11.4.1 using the ATP-5 analysis population.

2. The non-inferiority analysis of placebo versus azithromycin with respect to clinical improvement at Visit 4 (as defined in Section 3.2.1), using a non-inferiority margin of 12.5%, will be repeated as described in Section 11.4.1 using the ITT analyses population as well as ATP-11 analysis population.

3. The non-inferiority analysis of placebo versus azithromycin with respect to clinical improvement at Visit 5 (as defined in Section 3.2.1), using a non-inferiority margin of 12.5%, will be repeated as described in Section 11.4.1 using the ITT analyses population as well as ATP-28 analysis population.

4. Using the ATP-11 and ATP-28 analysis populations, respectively, the mean number of days of antibiotic use from Day 1 until Visit 4 or Visit 5 will be computed for placebo versus azithromycin, in addition to an estimated difference in means and associated 95% confidence intervals. The significance of the difference in means will be tested by a t-test.

5. Using he ATP-11 and ATP-28 analysis populations, respectively, the proportion of subjects with one or more return visits to a physician's office or urgent care for persistent or worsening LRTI at any time after randomization by Visit 4 or by Visit 5 will be

computed for placebo versus azithromycin, in addition to an estimated odds ratio and associated 95% confidence intervals. The significance of the difference in proportions will be tested by a Fisher's Exact Test.

6. Using he ATP-11 and ATP-28 analysis populations, respectively, the proportion of subjects with one or more emergency department visits for persistent or worsening LRTI at any time after randomization by Visit 4 or by Visit 5 will be computed for placebo versus azithromycin, in addition to an estimated odds ratio and associated 95% confidence intervals. The significance of the difference in proportions will be tested by a Fisher's Exact Test.

7. Using the subsets of the ATP-11 and ATP-28 analysis populations, respectively, consisting of subjects not hospitalized at the enrollment and randomization visit, the proportion of subjects with one or more hospitalizations for persistent or worsening LRTI at any time after randomization by Visit 4 or by Visit 5 will be computed for placebo versus azithromycin, in addition to an estimated odds ratio and associated 95% confidence intervals. The significance of the difference in risk will be tested by a Fisher's Exact Test.

8. Using the ATP-11 and ATP-28 analysis populations, respectively, the proportions of subjects exhibiting improvement in at least one presenting symptom (Table 1) by Visit 4 or by Visit 5 will be computed for placebo versus azithromycin, in addition to an estimated odds ratio and associated 95% confidence intervals. 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.

9. The Day 5 DOORs (an ordinal outcome defined in Section 3.2.3) will be compared between the placebo and azithromycin arms. The sum of the probability that a randomly selected subject will have a better DOOR if assigned to the placebo arm plus one-half the probability of equal DOORs will be estimated. The null hypothesis to be tested is that the probability is equal to 0.50 (lack of superiority of azithromycin therapy). The analysis will be carried out using the ITT analysis population, with missing DOOR values (treated as continuous) imputed using multiple imputation, utilizing linear regression models. The analysis will be repeated using the ATP-5 population. At minimum, the imputation model will utilize available information collected at baseline and any completed study visits. Further details of the imputation model will be described in the SAP. The Mann-Whitney U statistic will be combined across the imputed datasets to give the test statistic and Rubin's Rules used to define distribution of the test statistic under the null hypothesis. A point estimate of the estimand will be computed by dividing combined test statistic by the number of pairwise comparisons and a 95% confidence interval of the estimand will be computed by inverting the described test of the null hypothesis.

10. Using the ATP-5 analysis population, forest plots of 95% confidence intervals for the difference in proportions of subjects with each solicited event (a component of DOOR) collected through Visit 3, for each severity threshold (mild or greater, moderate or greater, or severe) will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

11. Using the ATP-5 analysis population, a forest plot of 95% confidence intervals for the difference in proportions of subjects with 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 (a component of clinical improvement and DOOR) will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

12. Using the ATP-5 analysis population, for each qualifying vital sign (temperature, pulse, respiratory rate, or pulse oximetry) and symptom (cough, sputum production, chest pain, or difficulty breathing), improvement in the sign or symptom at Visit 3 compared to baseline in subjects with the symptom or vital sign abnormality at baseline (a component of clinical improvement and DOOR) will be analyzed. A forest plot of 95% confidence intervals for the difference in proportions of subjects with improvement in the symptom or sign will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

13. Using the ATP-5 analysis population, for each qualifying symptom (cough, sputum production, chest pain, or difficulty breathing), deterioration in the symptom at Visit 3 compared to baseline (a component of clinical improvement and DOOR) will be analyzed in subjects having the symptom at baseline. A forest plot of 95% confidence intervals for the difference in proportions of subjects with deterioration in the symptom will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

14. Using the ATP-5 analysis population, for each vital sign (temperature, pulse, respiratory rate, or pulse oximetry), new occurrence of a vital sign abnormality at Visit 3 compared to baseline (a component of clinical improvement and DOOR) will be analyzed in subjects without the sign abnormality at baseline. Additionally, the proportion of subjects with fever in the 24 hours preceding or at Visit 3 (fever is defined as ≥37.8 °C or 100.0 °F, measured anywhere on the body), unless related to a new process that is unrelated to the prior diagnosis of LRTI will be analyzed. A forest plot of 95% confidence intervals for the difference in proportions of subjects with new occurrence of a sign abnormality at Visit 3 compared to baseline or fever in the 24 hours preceding or at Visit 3 will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

11.4.3 Exploratory Analyses

1. Using the ATP-5 analysis population, mean changes in PCT levels at Visit 3 relative to baseline will be computed for placebo versus azithromycin, in addition to an estimated difference in mean PCT changes and associated 95% confidence intervals. Significance of a difference in mean PCT changes between treatment groups will be tested by a Wilcoxon test. Details of the analysis will be described in the SAP.

2. Using the ATP-5 analysis population, logistic regression will be used to test whether changes in PCT levels at Visit 3 relative to baseline are associated with clinical improvement at Visit 3, after accounting for treatment assignment.

3. The Day 11 DOORs (an ordinal outcome defined in Section 3.2.3) will be compared between the placebo and azithromycin arms. The sum of the probability that a randomly selected subject will have a better DOOR if assigned to the placebo arm plus one-half the probability of equal DOORs will be estimated. The null hypothesis to be tested is that the probability is equal to 0.50 (lack of superiority of azithromycin therapy). The analysis will be carried out using the ITT analysis population, with missing DOOR values (treated as continuous) imputed using multiple imputation, utilizing linear regression models. The analysis will be repeated using the ATP-11 population. At minimum, the imputation model will utilize available information collected at baseline and any completed study visits. Further details of the imputation model will be described in the SAP. The Mann-Whitney U statistic will be combined across the imputed datasets to give the test statistic and Rubin's Rules used to define distribution of the test statistic under the null hypothesis. A point estimate of the estimand will be computed by dividing combined test statistic by the number of pairwise comparisons and a 95% confidence interval of the estimand will be computed by inverting the described test of the null hypothesis.

4. Using the ATP-11 analysis population, forest plots of 95% confidence intervals for the difference in proportions of subjects with each solicited event (a component of DOOR) collected through Visit 4, for each severity threshold (mild or greater, moderate or greater, or severe) will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

5. Using the ATP-11 analysis population, a forest plot of 95% confidence intervals for the difference in proportions of subjects with 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 (a component of clinical improvement and DOOR) will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

6. Using the ATP-11 analysis population, for each qualifying symptom (cough, sputum production, chest pain, or difficulty breathing) and for fever, improvement in the symptom or fever at Visit 4 compared to baseline in subjects with the symptom or fever will be

analyzed. A forest plot of 95% confidence intervals for the difference in proportions of subjects with improvement in the symptom or fever will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

7. Using the ATP-11 analysis population, for each qualifying symptom (cough, sputum production, chest pain, or difficulty breathing), deterioration in the symptom at Visit 4 compared to baseline will be analyzed in subjects having the symptom at baseline. A forest plot of 95% confidence intervals for the difference in proportions of subjects with deterioration in the symptom will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

8. Using the ATP11 analysis population, the proportion of subjects with fever in the 24 hours preceding or at Visit 4 (fever is defined as ≥37.8 °C or 100.0 °F, measured anywhere on the body), unless related to a new process that is unrelated to the prior diagnosis of LRTI will be analyzed. A forest plot of 95% confidence intervals for the difference in proportions of subjects with fever in the 24 hours preceding or at Visit 4 will be generated. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a DMID-sponsored, DMID-affiliated or manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), DMID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, each participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. Each site principal investigator will provide direct access to all trial-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. Each site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement quality control procedures for the data entry system and generate database quality control checks. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

The VIDAS®3 Instruments and VIDAS® B.R.A.H.M.S Procalcitonin (PCT) have been commercialized in US. Both products used in this trial will be labeled with investigational use only (IUO) but they are manufactured with quality assured using the same standards with the commercialized products. Prior to the trial testing, the VIDAS®3 Instruments will be qualified by field service engineers (FSE) from bioMerieux to ensure that the instruments meet all the requirements. There will be routine maintenance to be performed by the testing lab to ensure that the instruments are under good condition. The instruments will also be checked annually by FSE from bioMerieux as annual maintenance. bioMerieux will provide support on any issues and anomalies during the trials through remote or on-site assistance.

VIDAS® B.R.A.H.M.S PCT testing are ensured by both calibration before the initiation of the trial testing and every 28 days during the trial. Internal controls are included in each patient sample testing run to provide validation of testing results of the specific run.

If any of the following situations identified, repeat testing should be performed:

- In the event of invalid control(s), the entire run must be repeated. Only the valid repeat result will be taken into account.
- In the event of established human error, or if the system does not give any results, repeat testing will be performed. Only the valid repeat result will be taken into account.

More details can be found in the product insert.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The site principal investigator will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site principal investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

14.2 Institutional Review Board

Prior to enrollment of subjects into this trial, the approved protocol and informed consent form will be reviewed and approved by the appropriate IRB listed on its FWA.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial and a copy will be provided to DMID. The IRB Federal Wide Assurance number will be provided to DMID.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the site principal investigator for submission to the IRB prior to implementation.

14.3 Informed Consent Process

The site principal investigator will choose subjects in accordance with the eligibility criteria detailed in Section 5. Before any study procedures are performed, subjects must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, subjects will receive a comprehensive explanation of the proposed study procedures and study interventions/products, including the nature and risks of the trial, alternate therapies, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information. Subjects will be allowed sufficient time to consider participation in the trial, after having the nature and risks of the trial explained to them, and have the opportunity to discuss the trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Informed consent forms describing in detail the study interventions/products, study procedures, risks and possible benefits are given to subjects. The informed consent form must not include any exculpatory statements. Informed consent forms will be IRB-approved and subjects will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site principal investigator (or designee) will explain the research study to subjects and answer any questions that may arise. Subjects must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the trial, including administering study product.

DMID will provide the site principal investigator, in writing, any new information that significantly impacts the subjects' risk of receiving the investigational product. This new information will be communicated by the site principal investigator to subjects who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site clinical staff may pre-screen via chart review and refer potential subjects to the research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

Subjects will be given a copy of all informed consent forms that they sign. By signing the informed consent form, subjects agree to complete all evaluations required by the trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from the trial for any reason.

The rights and welfare of subjects will be protected by emphasizing to subjects that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

14.3.1 Informed Consent/Assent Process (in Case of a Minor or others unable to consent for themselves)

N/A

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study is focused on individuals aged 18 or greater of all racial, ethnic, and gender/sex categories.

14.5 Subject Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the Sponsor and all data and information generated by the participating site as part of the trial (other than a subject's medical records) will be kept confidential by the site principal investigator and other study personnel to the extent permitted by law. This information and data will not be used by the site principal investigator or other study personnel for any purpose other than conducting the trial. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site principal investigator or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of the trial (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 16.

The study monitor, applicable regulatory authorities, such as the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

14.6 Study Discontinuation

If the trial is discontinued, subjects who sign the informed consent form, and are randomized and treated will continue to be followed for safety assessments. No further study treatment will be administered.

14.7 Future Use of Stored Specimens

Subjects will be asked for permission to keep any samples for use in future research studies. Samples may be stored temporarily at the local site or longer term at DMID CMS central clinical storage facility. Samples may be shared with other investigators at other institutions, provided that appropriate human subject protection plans are in place and DMID has been consulted and approved of the use. The samples will not be sold or used directly for production of any commercial product. No human genetic tests (i.e., DNA testing) will be performed on samples, although measures of gene expression may be performed. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject's confidentiality.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subject's samples will not be kept in their health records.

Subjects may be given the option to decide if they want their samples to be used for future research or have their samples destroyed at the end of the trial. The subject's decision can be changed at any time prior to the end of the trial by notifying the study doctors or nurses in writing. However, if the subject originally consents to future use and subsequently changes his/her decision, any data from a previously collected sample may still be used for this research.

15 DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

Data collection forms will be derived from the eCRFs and provided by the SDCC to the sites to record and maintain data for each subject enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF should be consistent with the data collection form/source documents or the discrepancies should be documented.

The sponsor and/or its designee will provide guidance to investigators on making corrections to the data collection forms and eCRFs.

15.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

Emmes will serve as the Statistical and Data Coordinating Center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

15.2 Data Capture Methods

Clinical data (including solicited events, UADEs, and concomitant medications) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by Emmes. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

15.3 Types of Data

Data for this study will include clinical, laboratory, safety, and outcome measures.

15.4 Timing/Reports

A final report will be prepared following the availability of all the safety and efficacy data. Interim safety reports may be generated for the DSMB safety review.

After full analysis and final reporting is complete, and upon request and DMID approval, the SDCC will provide the participating sites with a summary of results by treatment group and/or subject treatment assignments. In this regard, the participating sites requesting such information to share with study subjects must do so in compliance with their respective IRB guidelines.

15.5 Study Records Retention

Records and documents pertaining to the conduct of this study, including data collection forms, source documents, consent forms, laboratory test results, and medication inventory records shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The site must contact DMID for authorization prior to the destruction of any study records. Informed consent forms for future use will be maintained as long as the sample exists.

15.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via the Emmes IDES

All deviations from the protocol must be addressed in study subject source documents. A completed copy of the DMID Protocol Deviation Form (IDES form) must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to

the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

16 PUBLICATION POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal.

17 LITERATURE REFERENCES

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Appendix A: 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						

Footnotes:

* 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. Any symptomatic treatment received on the day of/during the enrollment visit will not be recorded unless it is a non-study systemic antibiotic.