A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)

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IND Sponsor: NIH/NIAID/DMID

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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 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- 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 United States of America (US) federal regulations and ICH guidelines.

_____

Site Principal Investigator Signature

Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ARLG	Antibiotic Resistance Leadership Group
ATP	According-to-Protocol
CAP	Community Acquired Pneumonia
CAR	Clinical Agents Repository
CC	Complete Case
CFR	Code of Federal Regulations
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOOR	Desirability of Outcome Ranking
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EHR	Electronic Health Record
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDES	Internet Data Entry System
IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-to-Treat
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RADAR	Response Adjusted for Days of Antibiotic Risk
SAE	Serious Adverse Event/Serious Adverse Experience
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
USP	United States Pharmacopeia

PROTOCOL SUMMARY

Title:	A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)
Phase:	IV
Population:	400 subjects aged 6-71 months of age with community acquired pneumonia (CAP)
Number of Sites:	5; Vanderbilt University VTEU (Vanderbilt, Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh), Cincinnati Children's Hospital Medical Center VTEU, Duke University VTEU
Study Duration:	25 months
Subject Participation Duration:	~1 month after beginning antibiotic therapy
Description of Agent or Intervention:	Oral suspensions of amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos
Objectives:	**Primary:** 1. To compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs. standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days) **Secondary:** 1. To compare the composite overall outcome (DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #2 (Study Day 22 +/- 3 days) 2. To compare the resolution of symptoms (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2

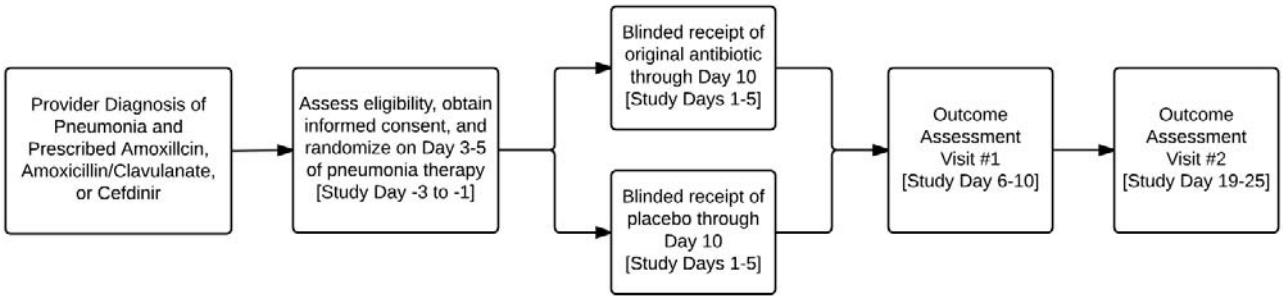
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
4. To compare solicited events (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
5. To compare medically attended visits to Emergency Departments (ED) or outpatient clinics, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics (components of the clinical response) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2

Exploratory:

1. To examine the robustness of results of DOOR comparisons when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

Description of Study Design:	Double-Blind, Placebo-Controlled, Randomized Trial
Estimated Time to Complete Enrollment:	24 months

Study Schematic:



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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The World Health Organization estimates 156 million cases of pneumonia occur annually in children <5 years of age.[1] In the United States (US), an estimated 1.5 million ambulatory visits for community-acquired pneumonia (CAP) in children occur annually.[2] Hospitalizations for CAP in children have decreased after the introduction of pneumococcal conjugate vaccine.[3] Further, in a pneumonia etiology study of >2500 children hospitalized with CAP in 3 US cities between 2010 and 2012, viral pathogens accounted for >70% of detections, while bacteria were identified in <20%.[4] However, ambulatory visits have not decreased, and pediatric CAP remains a very common infection for which antibiotics are generally prescribed.[2]

A 2011 Infectious Diseases Society of America (IDSA) guideline for management of CAP in children provides recommendations for antibiotic therapy.[5] Regarding the treatment duration for beta-lactam antibiotics, the guideline states "courses of 10 days have been best studied." Two studies conducted in resource-poor settings found no difference in outcomes between 3 vs. 5 days of oral therapy or 3 days of oral therapy vs. placebo for non-severe pneumonia.[6,7] However, these studies likely included many subjects with viral infection because substantial proportions had no radiographic findings or included children with wheezing. While stating "shorter courses may be just as effective," the IDSA guideline concluded there was insufficient evidence to recommend short course therapy.[5] The guideline identified clinical trials that provide information on the "shortest duration of therapy to decrease the development of antimicrobial resistance and the risk of antimicrobial toxicity" as a priority for future research.[5]

2.2 Rationale

In 2014, a randomized trial of short vs. standard course therapy in young children in Israel with CAP suspected to be of bacterial origin found a higher rate of treatment failure (40%) in subjects treated for only 3 days vs. subjects treated for 5 or 10 days.[8] The study was underpowered to detect a difference in treatment failure between subjects treated for 5 vs. 10 days, but treatment failure did not occur in either group.

The proposed study will test the effectiveness of short (5-day) vs. standard (10-day) course therapy in children who are diagnosed with CAP and initially treated in outpatient clinics, urgent care facilities, and emergency departments. The study will specifically address whether short course therapy is superior to standard therapy among children that have clinically improved since diagnosis. If superior to standard course therapy, short course therapy could reduce antibiotic exposure among young children. We will use a study methodology similar to the SCOUT Study ("Short Course Therapy for Urinary Tract Infections in Children")—a randomized, double-blind, placebo-controlled non-inferiority trial of short course antimicrobial therapy for urinary tract infection in children sponsored by NIAID through the "Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance" initiative. However, the SCOUT-CAP trial will use a superiority study design using an ordinal composite overall outcome (Desirability of Outcome Ranking, DOOR, see 3.2.1 Primary Outcome Measures)—to test the hypothesis that short

course (5 day) therapy is superior to standard course (10-day) beta-lactam therapy in children who have experienced early clinical improvement of pneumonia.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The potential risk of short course therapy is that clinical outcomes may not be equivalent to standard course therapy. Specifically, the percent of children with adequate clinical response (or in this case, no relapse of illness) may be lower in children receiving short course therapy. Adequate clinical response can be defined as resolution or substantial improvement in clinical signs and symptoms (e.g., fever, cough, respiratory rate, work of breathing) and the lack of need for additional antibiotic therapy, additional contacts with the health care system, or surgical procedures for worsening pneumonia. The magnitude of this risk is not well established, although a study from Israel suggests it is small[8]; nevertheless, this degree of risk will be evaluated during this trial.

2.3.2 Known Potential Benefits

If, as assessed by the primary outcome, short course therapy is superior to standard course therapy, short course therapy will reduce antibiotic exposure among children with CAP. The potential benefits of reduced antimicrobial exposure involve benefits both to the individual child and the population as a whole.

Potential benefits to the individual child include a simpler course of therapy, a lower risk of an adverse event associated with antibiotic therapy (e.g., antibiotic associated diarrhea, *Clostridium difficile* infection) and a lower risk of becoming colonized with antibiotic resistant bacteria.

Potential benefits to the population include a lower prevalence of colonization with pathogenic antibiotic resistant bacteria among children treated for CAP. Since these bacteria are transmissible, a lower prevalence of colonization among children treated for CAP confers a potential lower risk of colonization among all persons in the population, including children and adults regardless of whether they are treated with antibiotics.

3 OBJECTIVES

3.1 Study Objectives

Primary:

1. To compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days)

Secondary:

1. To compare the composite overall outcome (DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #2 (Study Day 22 +/- 3 days)
2. To compare the resolution of symptoms (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
4. To compare solicited events (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
5. To compare medically attended visits to Emergency Departments (ED) or outpatient clinics, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics (components of the clinical response) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2

Exploratory:

6. To examine the robustness of results of DOOR comparisons when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The primary endpoint/outcome measure is the DOOR at Outcome Assessment Visit #1.

DOOR is defined as follows:

I. Each subject is evaluated according to the ordinal composite outcome (See Table 1 below) and assigned an outcome rank ranging from 1-8.
II. Desirability of Outcome Ranking (DOOR) is then assigned according to two rules:
   (i) When comparing two subjects with different ordinal responses, the subject with a better ordinal response receives a higher rank.
   (ii) When comparing two subjects with identical ordinal responses, the subject with fewer days of antibiotic use receives a higher rank.

The ordinal composite outcome involves an assessment of whether the subject has an adequate clinical response and whether they have experienced any solicited events as defined below.

Table 1. Ordinal Outcome

	Adequate clinical response[1] (Assessed at Outcome Assessment Visits #1 and #2)	**Solicited events[3] (Assessed at Outcome Assessment Visits #1 and #2)**
1	Yes, with resolution of symptoms[2]	None
2	Yes, with resolution of symptoms[2]	Mild (Grade 1)
3	Yes, with resolution of symptoms[2]	Moderate (Grade 2)
4	Yes, with resolution of symptoms[2]	Severe (Grade 3)
5	Yes, with persistent symptoms of fever, tachypnea, or cough	None or any grade
6	No, with ED/clinic visit but no hospitalization	None or any grade
7	No, with hospitalization	None or any grade
8	Death from any cause	

[1]Adequate clinical response is defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.

- Persistent or worsening pneumonia is defined as receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
- Note: Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

[2]Resolution of symptoms is defined as the absence of all of the following:

- Oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding the Outcome Assessment Visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia;
- Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit;
- Presence of cough grade 2 or 3 at the Outcome Assessment Visit, defined as Grade 0 (no cough), Grade 1 (Occasional coughing [less than 4 times hourly]), Grade 2 (frequent coughing [4 or more times an hour], interferes with sleep), Grade 3 (almost constant coughing (never free of cough), makes sleep nearly impossible);

[3]Solicited events will be captured daily until Outcome Assessment Visit #1; thereafter, parents/legal guardians will report symptoms based on memory aid and medical interview by study staff. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Table 2. Solicited Events Grading

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Irritability	More irritable or fussy than usual but can be consoled; no interference with smiling/playing	Irritability or fussiness that is difficult to console and interferes with smiling and playing	Irritability or fussiness that lasts for more than 4 consecutive hours in a 24 hour period or cannot be consoled
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 occurring >6 times/day	Bloody diarrhea, or diarrhea that requires medical intervention, laboratory testing, or hospitalization
Allergic Reaction	Localized rash or pruritus without rash	Diffuse rash (maculopapular or urticarial)	Generalized rash consistent with Stevens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis; anaphylaxis; or angioedema
Stomatitis	Oral lesions associated with parenteral report of mild oral discomfort	Oral lesions associated with difficulty swallowing, but able to eat and drink	Oral lesions associated with inability to swallow solids or liquids; requires medical intervention, IV fluids, or hospitalization
Candidiasis	Mild mucocutaneous candidiasis or diaper dermatitis, with no treatment or topical treatment only	Moderate mucocutaneous candidiasis requiring oral antimicrobial treatment	Severe mucocutaneous candidiasis; requires medical intervention, intravenous treatment, or hospitalization

3.2.2 Secondary Outcome Measures

Secondary outcome measures include:

1. DOOR at Outcome Assessment Visit #2Resolution of symptoms (a component of DOOR) at each outcome assessment visit, defined as the absence of fever, tachypnea, or cough of grade 2 or higher.
2. Adequate clinical response rates (a component of DOOR) at each outcome assessment visit, defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
3. Frequency of solicited events at each outcome assessment visit, as listed in Table 2.
4. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for persistent or worsening pneumonia (as defined above) at each outcome assessment visit

i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.

5. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for all causes at each outcome assessment visit
   i. Individual event types (e.g., medical visits, hospitalizations surgical procedures, and receipt of non-study systemic antibiotic) will be compared between treatment groups.

3.2.3 Exploratory Outcome Measures

1. DOOR at Outcome Assessment Visits #1 and #2, when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

4 STUDY DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled, superiority clinical trial evaluating short course (5 day) vs. standard course (10 day) of oral beta-lactam antibiotic therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) for treatment of CAP in children 6-71 months of age who have clinically improved prior to enrollment. The study will randomize approximately 400 enrolled subjects to one of the two study arms (approximately 200 children in each arm) in order to reach 360 evaluable subjects. Subjects will be randomized (1:1) to receive either a standard course of the initially prescribed antibiotic (10 days) or a short course of the initially prescribed antibiotic (5 days) plus 5 days of matching placebo.

The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Day -5 is defined as the date on which oral beta-lactam therapy is initiated for a diagnosis of CAP. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. These subjects will be assessed for eligibility and enrolled on Day -3 to -1 of their initially prescribed oral beta-lactam therapy. Subjects may also be enrolled on Day 1 (the first day of receipt of study agent) provided they have not yet received any doses of the healthcare provider-prescribed antibiotic therapy for that day.

A Schedule of Events is provided in Appendix A.

Visit 1: Enrollment Visit. Subjects who meet the eligibility criteria, and whose parent/guardian consents for participation in the study, will complete an Enrollment Visit on Day -3 to -1. Subjects satisfying the inclusion criteria with no exclusion criteria will be enrolled and randomized. Enrolled subjects will continue to receive the initially prescribed antibiotic through Day -1. The subjects' parents/guardians will be instructed to contact study personnel if their child develops fever or worsening respiratory symptoms (worsening cough, increased work of breathing, any other concerning symptoms in the parents' estimation) following enrollment.

Randomization: Enrolled subjects will be randomized to short vs. standard course therapy at a 1:1 ratio, with stratification by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility).

Intervention: Subjects will continue on the initially prescribed antibiotic through Day -1, until they have completed 5 days (i.e., 5 scheduled doses of once daily medication, 10 scheduled doses of twice daily medication) of antibiotic therapy [e.g., if a subject takes the first dose of antibiotic in the afternoon of Day -5, the first dose of study agent would occur on the afternoon of Day 1, providing 10 total scheduled doses of a twice daily prescribed antimicrobial]. The first day of receipt of study agent will be Day 1. Subjects assigned to standard course therapy will receive 5 additional days (10 doses) of the same initially prescribed antibiotic, with standardized twice-daily dosing. Subjects assigned to short course therapy will receive 5 more days (10 doses) of a matching placebo. Both the study agent and placebo may appear different than the commercial formulation the child originally received. The placebo will appear indistinguishable in color, taste, thickness, and consistency as the active antibiotic the child would otherwise receive

in the study. The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation.

Follow-up and Assessment of Endpoints: Subjects will be scheduled for the following assessment visits:

Visit 2: Outcome Assessment Visit #1, Day 6 to 10 (1-5 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Visit 3: Outcome Assessment Visit #2, Day 19 to 25 (14-20 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects who are identified as having an inadequate clinical response prior to Outcome Assessment Visit #1 will be asked to complete Outcome Assessment Visits #1 and #2, in order to evaluate the occurrence of any solicited events and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects will be invited to contribute oropharyngeal and stool specimens at specified times throughout the study for future use (see Appendix A, Schedule of Events). Additional informed consent will be obtained for future use sample collection.

5 STUDY ENROLLMENT AND WITHDRAWAL

Subjects who are diagnosed with CAP in EDs, urgent care facilities, and clinics will be screened for eligibility. Screening will continue until 400 subjects are enrolled cumulatively across all the study sites. The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on antibiotic therapy using oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. Other forms and/or mechanisms of recruitment may also be used. The local IRB will approve recruitment materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

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

Eligible subjects may be included in the study if they meet ALL of the following criteria at the Enrollment Visit (Day -3 to -1):

1. Age 6 – 71 months
2. Provider diagnosis of CAP and prescription of antibiotic therapy with amoxicillin[1], amoxicillin-clavulanate[1], or cefdinir[2]

   [1] amoxicillin or amoxicillin-clavulanate prescribed at an amoxicillin dose of at least 60 mg/kg/day, maximum 4000 mg/day.

   [2] cefdinir (prescribed at a minimum dose of 10 mg/kg/day, maximum 600 mg/day).
3. Parental report of clinical improvement[3]

   [3] based on lack of oral, rectal, axillary, or tympanic temperature ≥38.3°C for ≥24 hours; current respiratory rate no greater than 50 breaths/minute (<2 years of age) or 40 breaths/minute (≥ 2 years of age); and current grade of cough <3.
4. Ability of a parent or guardian to understand and comply with the study procedures and be available for all study visits
5. Signed written informed consent by a parent or guardian

5.2 Subject Exclusion Criteria

Subjects will be excluded from the study if they meet ANY of the following criteria:

1. Treatment with any systemic antibiotic therapy within 7 days before the diagnosis of CAP

2. Initial therapy for CAP with combination antibiotic therapy[4]

   [4] *amoxicillin, amoxicillin/clavulanate or cefdinir plus one or more additional oral, intravenous, or intramuscular antibiotics*

3. History of anaphylaxis or severe drug allergy to amoxicillin, if prescribed amoxicillin or amoxicillin/clavulanic acid; or oral cephalosporin antibiotics (except cefaclor), if prescribed cefdinir
4. Presence of concomitant bacterial infection that requires >5 days of antibiotic therapy
5. Radiographic findings (where applicable) of complicated pneumonia (pleural effusion, lung abscess, or pneumatocele) at presentation or any subsequent chest radiograph up to the time of enrollment
6. Hospitalization for pneumonia during Day -5 to -1 of antibiotic therapy for CAP
7. Pneumonia due to *S. aureus* or group A streptococcus documented by positive blood culture or PCR, at the time of enrollment.
8. History of pneumonia within the previous 6 months
9. History of bronchodilator or inhaled corticosteroid use in the preceding 6 months
10. Provider-diagnosis of aspiration pneumonia, bronchiolitis, bronchitis, or acute asthma exacerbation[5]

    [5] *Single, trial-dose of an inhaled bronchodilator at the time of pneumonia diagnosis will not satisfy this exclusion.*

11. Surgery or other invasive procedures of the upper or lower airway (e.g., bronchoscopy, laryngoscopy) with general anesthesia or hospitalization ≤7 days before diagnosis of CAP
12. History of an underlying chronic medical condition[6]

    [6] *including chronic heart disease, chronic lung disease (includes asthma with the exception of mild, intermittent asthma),congenital anomalies of the airways or lung, cystic fibrosis, chronic renal disease including nephrotic syndrome, protein-losing enteropathy of any cause, severe malnutrition, genetic syndromes, neurocognitive disorders, or metabolic disorders (including phenylketonuria)*

13. History of a condition that compromises the immune system[7]

    [7] *HIV infection, primary immunodeficiency, anatomic or functional asplenia; receipt of a hematopoietic stem cell or solid organ transplant at any time; receipt of immunosuppressive therapy including chemotherapeutic agents, biologic agents, antimetabolites or radiation therapy during the past 12 months; or daily use of systemic corticosteroids for more than 7 consecutive days during the past 14 days.*

14. Any other condition that in the judgment of the investigator precludes participation because it could affect the safety of the subject
15. Current enrollment in another clinical trial of an investigational agent
16. Previous enrollment in this trial

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Per International Conference 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. Subjects will be assigned to either placebo or active study drug (the same antibiotic that they were prescribed for the first 5 days of treatment). After a subject is enrolled, they will be given a random treatment assignment of study product to either short course or standard course therapy. Randomization to short vs. standard course therapy will be at a 1:1 ratio (approximately 200 subjects per treatment group). Subjects will be stratified by age group <24 months vs. 24-71 months), type of initial antimicrobial therapy, and initial treatment in an ED or outpatient clinic/urgent care center.

Enrollment of subjects will be performed online using AdvantageEDC. The list 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 volunteer a treatment code from the list after the necessary data have been entered into the system. A designated individual 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.

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.

5.3.2 Masking Procedures

This is a double-blind clinical trial. The study subjects and their parents/guardians, investigators, and study team staff will remain blinded to study treatment assignment throughout the study. The subjects and their families, investigators, and study team staff will not be blinded to which of the three antibiotics (amoxicillin, amoxicillin-clavulanate, cefdinir) the subject was initially prescribed.

The study products and placebo will be prepared by the unblinded site Research Pharmacist. Only the preparing pharmacist will be aware of the study product bottle assignments. For subjects randomized to standard course therapy, the pharmacy will provide the same medication prescribed initially. For subjects randomized to short course therapy, the pharmacy will provide a placebo that resembles the appearance (color and texture), flavor, and consistency of the active study product. All study products will be packaged with an identical appearance. Additional details regarding dispensing procedures will be included in the protocol-specific MOP.

The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation. The unblinded site Research Pharmacist

will be the only person to perform the unmasking if needed. Additional details regarding labeling procedures will be included in the protocol-specific MOP.

During the consenting process it will be explained to the parents of any potential subjects that the study product (treatment or placebo) that will be provided for administration after Day 5, may or may not taste exactly the same as the originally prescribed medication, and that the look and smell may be slightly different because it might be supplied by a different manufacturer than that of the initially prescribed antibiotic. Parents will also be instructed that the amount or frequency of the prescribed study product has been made uniform across all study groups; therefore, the amount/frequency may be different than originally prescribed by their provider (e.g., receipt of once daily cefdinir is not excluded, but upon study entry, those subjects will receive either twice daily cefdinir or placebo).

5.3.3 Reasons for Withdrawal

Subject Withdrawal
Subjects' parents/guardians 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
- Any new information becomes available that makes further participation unsafe.

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

Discontinuation of Treatment
A subject may be discontinued from treatment and continue to be followed if any of individual halting rules, as defined in Section 9.5.2, are met.

5.3.4 Handling of Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Parents/guardians will be encouraged to complete the Early Termination Visit, as listed in Section 7.5. Unless they expressly state that they wish to have no additional follow-up or data collection, subjects who withdraw from the study will receive a follow-up phone call approximately one week after their withdrawal. This will allow the site to assess the status of the subject and determine if any medical follow up care was sought. Although subjects are free to withdraw at any time or may be withdrawn by the site PI or appropriate sub-investigator at any time, subjects will be encouraged to remain in this study for follow-up assessments (may be by telephone rather than in person) continuing through approximately 1 month after study treatment.

Every attempt will be made to follow all ongoing solicited events or serious adverse events, as well as new-onset chronic medical conditions, to resolution or until the subject's condition becomes stable.

Subjects who discontinue treatment will be followed according to the study protocol and will not be replaced.

5.3.5 Termination of Study

The National Institute of Allergy and Infectious Diseases (NIAID), the IRB of record, or the FDA 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 would 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

Amoxicillin
Amoxicillin, USP is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is similar to penicillin in its bactericidal action against susceptible bacteria during the stage of active multiplication. It acts through the inhibition of cell wall biosynthesis that leads to the death of the bacteria.

Amoxicillin-Clavulanate
Amoxicillin-Clavulanate is an oral antibacterial combination consisting of semisynthetic antibiotic amoxicillin and the beta-lactamase inhibitor, clavulanate potassium. Clavulanic acid is particularly active against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins.

Cefdinir
Cefdinir is an extended-spectrum, semisynthetic cephalosporin. Bactericidal activity of cefdinir results from inhibition of cell wall synthesis and is stable in the presence of some, but not all, beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

6.1.1 Acquisition

Amoxicillin, Amoxicillin-Clavulanate, and Cefdinir will be obtained by the DMID Clinical Agents Repository (CAR, Fisher BioServices). The matching placebo for each active drug will be will be prepared by a compounding pharmacy (Bayview Pharmacy) and stored at the DMID CAR.

Bayview Pharmacy will perform the compounding, filling, packaging and labeling of study drug placebos according to applicable regulatory requirements. All active study drugs and placebos will be acquired through the DMID Clinical Agents Repository (CAR, Fisher BioServices).

Study product (amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos) will be shipped from the DMID CAR to the study site upon request and approval by DMID.

6.1.2 Formulation, Packaging, and Labeling

6.1.2.1 Amoxicillin

Amoxicillin will be supplied as an oral powder for suspension in the following strengths: 200mg/5mL and 400mg/ 5mL packaged in 100mL bottles. The 200mg/5mL strength contains 200mg of amoxicillin as the trihydrate in each 5mL of reconstituted suspension. The 400mg/5mL strength contains 400mg of amoxicillin as the trihydrate in each 5mL of reconstituted suspension.

The lower strength (200mg/5mL) will be used in the lower weight bands (or as originally prescribed prior to enrollment) and the higher strength (400mg/5mL) will be used in the higher

weight bands (or as originally prescribed prior to enrollment) as described in the protocol-specific MOP.

6.1.2.2 Placebo for Amoxicillin

Placebo will be supplied as matching liquid for each of the active strengths provided. In order to maintain the blind, the liquid placebo will be formulated for the same appearance (color and texture), flavor and consistency as the active study drug and will be provided in 100mL bottles.

6.1.2.3 Amoxicillin-Clavulanate

Amoxicillin-clavulanate will be supplied as an oral powder for suspension in the following strengths: 200mg/ 5mL and 400mg/ 5mL packaged in 100mL bottles. The 200mg/5mL strength contains 200mg of amoxicillin and 28.5mg of clavulanic acid as a potassium salt in each 5mL of reconstituted suspension. Each 5mL of the 200mg/5mL strength contains 0.14mEq of potassium. The 400mg/ 5mL strength contains 400mg of amoxicillin and 57mg of clavulanic acid as a potassium salt in each 5mL of reconstituted suspension. Each 5mL of the 400mg/ 5mL strength contains 0.29mEq of potassium. The 200mg/ 5mL and 400mg/ 5mL formulations contain aspartame and should not be used by phenylketonurics.

The lower strength (200mg/5mL) will be used in the lower weight bands (or as originally prescribed prior to enrollment) and the higher strength (400mg/5mL) will be used in the higher weight bands (or as originally prescribed prior to enrollment) as described in the protocol-specific MOP.

6.1.2.4 Placebo for Amoxicillin-Clavulanate

Placebo will be supplied as matching liquid for each of the active strengths provided. In order to maintain the blind, the liquid placebo will be formulated for the same appearance (color and texture), flavor and consistency as the active study drug and will be provided in 100mL bottles.

6.1.2.5 Cefdinir

Cefdinir will be supplied as a white to off-white oral powder for suspension in the following strengths: 125mg/ 5mL and 250mg/ 5mL packaged in 100mL bottles. The 125mg/ 5mL strength contains 125mg of cefdinir in each 5mL of reconstituted suspension. The 250mg/ 5mL strength contains 250mg of cefdinir in each 5mL of reconstituted suspension. Each 5mL of the 250mg/ 5mL strength contains 1.37g of sucrose and each 5mL of the 125mg/5mL strength contains 1.5g of sucrose. Certain formulations from different manufacturers may contain up to 2.86g of sucrose per 5mL.

The lower strength (125mg/ 5mL) will be used in the lower weight bands (or as originally prescribed prior to enrollment) and the higher strength (250mg/ 5mL) will be used in the higher weight bands (or as originally prescribed prior to enrollment) as described in the protocol-specific MOP.

6.1.2.6 Placebo for Cefdinir

Placebo will be supplied as matching liquid for each of the active strengths provided. In order to maintain the blind, the liquid placebo will be formulated for the same appearance (color and texture), flavor and consistency as the active study drug and will be provided in 100mL bottles.

6.1.2.7 Packaging and Labeling

The active study drug will be supplied in their original manufacturer's bottles. The placebo supplied for each active study drug will be filled and packaged by the compounding pharmacy. Each container will also be labeled in compliance with applicable regulatory requirements, including the FDA-required cautionary statement *"Caution- New drug -Limited by Federal (or United States) Law to Investigational Use Only."* As per Section 6.2.2, at the time of study product preparation, the site pharmacist will transfer the contents of the active and placebo into identical containers and affix with blinded labels for dispensing to the subject.

6.1.3 Product Storage and Stability

6.1.3.1 Amoxillin

Store dry powder at 20˚C to 25˚C (68˚F to 77˚F) [See USP Controlled Room Temperature] for unreconstituted powder

Upon reconstitution, when stored under refrigeration or room temperature, any remaining or unused portion must not be used after 14 days. Refrigerated storage is preferred, but not required.

6.1.3.2 Placebo for Amoxicillin

Store the suspension at 2°C to 8°C.

To maintain the blind, upon dispensing, parents/caregivers will be given the same storage instructions as the active drug.

6.1.3.3 Amoxicillin-Clavulanate

Store dry powder at 20˚C to 25˚C (68˚F to 77˚F) [See USP Controlled Room Temperature].

Upon reconstitution, the suspension must be stored under refrigeration and any remaining or unused portion must not be used after 10 days

6.1.3.4 Placebo for Amoxicillin-Clavulanate

Store the suspension at 2°C to 8°C.

To maintain the blind, upon dispensing, parents/caregivers will be given the same storage instructions as the active drug.

6.1.3.5 Cefdinir

Store dry, unsuspended powder at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

Upon reconstitution, the suspension must be stored at room temperature and any remaining or unused portion must not be used after 10 days.

6.1.3.6 Placebo for Cefdinir

Store the suspension at 2°C to 8°C.

To maintain the blind, upon dispensing, parents/caregivers will be given the same storage instructions as the active drug.

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

6.2.1 Dosage

Subjects will complete five days of their originally prescribed antibiotic and then take 5 days of the study product, as follows:

Amoxicillin and Amoxicillin-Clavulanate

Amoxicillin and Amoxicillin-Clavulanate will be dosed based on the amoxicillin component as 80-100 mg/kg/day (maximum 2000 mg/day) divided twice daily.

The matching placebo will be dosed at the same volume calculated for the active dose.

Cefdinir

Cefdinir will be dosed as 12-16 mg/kg/day (maximum 600mg/ day) divided twice daily.

The matching placebo will be dosed at the same volume calculated for the active dose.

6.2.2 Preparation

The site Research Pharmacist must be unblinded and will prepare the active and placebo study products for dispensing to the subject.

Instructions for reconstitution of each active drug will be provided in the protocol-specific MOP. Upon reconstitution, active amoxicillin, amoxicillin-clavulanate, and cefdinir will be transferred from their original commercial containers into new containers strictly for blinding/masking purposes. The matching placebo liquid will be transferred into identical containers to maintain the blind.

Additional details regarding subsequent labeling, preparation of kits, and procedures for dispensing or administration of study product will be described in the protocol-specific MOP.

6.2.3 Administration

All active and placebo study products will be orally administered via oral dosing syringe or dosing cup. For older children in whom a dosing cup is preferred, parents will be instructed to measure the drug in the oral dosing syringe prior to transferring to the dosing cup.

6.3 Modification of Study Intervention/Investigational Product for a Participant

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)

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 will be retained until monitored and released for disposition as per the Sponsor.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

The investigator will maintain records documenting all study products administered to each subject for the entire study period. Subjects will be asked to complete a memory aid and bring their study product containers. The memory aid will be used to record daily study medication taken, concomitant medications (e.g., pain medication), temperature, solicited events, and presence of cough. The study coordinator/investigator will document any missed doses of study medication and provide counseling per study sites' routine procedures to promote compliance with study medication. 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 medication compliance will be obtained by parental interview. The study coordinator/investigator will record how study drug compliance information was obtained. In addition, study product containers will be collected for the purpose of maintaining drug accountability. Once study accountability is completed by the study monitor, used/opened study product bottles may be discarded.

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 through the last study visit or early termination. 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 chronic medical disease or condition.

Medications that might interfere with the evaluation of the study product or may compromise participant 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 affiliated with the study clinical trial centers. Providers will be informed about the study and provided with site-specific SCOUT-CAP provider information pamphlets summarizing the study design and participant eligibility criteria. Providers may also be asked to alert their patients about their practice's participation in the SCOUT-CAP 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 new pneumonia cases from medical records.

Once a potentially eligible subject with the diagnosis of CAP is identified, study staff will first contact the treating clinic to confirm willingness to have the patient participate in the study. For subjects deemed potentially eligible, study staff will attempt to contact the parent(s)/guardian(s) by telephone. If the parent(s)/guardian(s) are contacted successfully, the study staff may use the telephone contact guide (see MOP). Study staff will explain the study protocol and describe the inclusion/exclusion criteria. Study staff will answer any questions and concerns the parent(s)/guardian(s) may have. If the parent(s)/guardian(s) are interested in the study, study staff will schedule the Enrollment Visit on Day -3 to Day -1 of antibiotic therapy.

Parents/caregivers of potential subjects who express interest in participation will be contacted again by study staff prior to the Enrollment Visit to confirm the appointment time and location and to assess the presence of ongoing symptoms such as fever, respiratory rate, and cough. If fever, elevated respiratory rate, or Grade 3 cough are present, the visit may be rescheduled for a later day, but no later than before receipt of the first dose of their initially prescribed antibiotic on the sixth consecutive calendar day of treatment. In all instances, the parent/guardian will be instructed to continue administration of original antibiotic as instructed by the treating clinician until the Enrollment Visit.

7.2 Enrollment/Baseline

At the Enrollment Visit, study staff will obtain written informed consent from the parent(s)/guardian(s) for the primary study and request consent for collection of throat swabs and stool specimens for future use. Declination to participate in collection of future use samples will not affect participation in the primary study. After the parent/guardian has had the opportunity to ask questions and has signed the informed consent document, the following activities will be performed by the study staff:

- Eligibility criteria will be reviewed;
- A complete medical history and sociodemographic data will be obtained by interview with the subject's parent(s)/legal guardian;

- A physical assessment will be performed to determine general appearance, hydration status; vital signs, including temperature, heart rate, and respiratory rate; an assessment of work of breathing; and presence of skin rash; additionally, if indicated by the physical assessment or medical history, a physical examination by a study clinician may occur;

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

- An initial assessment of clinical response will be obtained to include maximum temperature in the past 24 hours and an assessment of improved activity and appetite since initiating antibiotic therapy;

- All concomitant medications taken within 30 days of signing the informed consent form will be recorded;

- Subjects who meet eligibility criteria will be enrolled in AdvantageEDC^{SM} and randomly assigned to one of two arms: standard course therapy (5 days of active medication) vs. short course therapy (5 days of matching placebo);

- Study product will be dispensed and study staff will review the study product with the subject's family and review the study product storage and dosing instructions;

- Subjects will be provided with a memory aid and other study-related materials to record daily temperature, solicited events, concomitant medications, presence of cough, and daily dose administration. Parents will be instructed that any temperatures over 100.9˚F should be repeated 15 minutes later in the same manner as the initial temperature. Study staff will instruct the parent/guardian to complete the memory aid in order to document adherence and to bring the medication bottle with them to the Outcome Assessment Visit #1. Study staff will also review the memory aid used to assess specific, solicited events;

- Collection of a throat swab specimen if contributing future use samples;

- Dispense containers for collection of a stool specimen, if participating in future use portion of the study.

Since the Enrollment Visit will occur during Day 3-5 of treatment (Day -3 to -1), the subject will be instructed to complete the originally prescribed medication through Day -1 (after receipt of the last dose of the originally prescribed medication on the fifth consecutive calendar day of treatment) and to start study product on Day 1.

Parents will be educated at the time of their child's enrollment in the study about prompt and adequate treatment for recurrence of symptoms or solicited events. The subject's parent/guardian will be instructed to contact their primary care provider as soon as possible in the event of worsening respiratory status, recurrence of fever, or for other concerns. Parents/guardians will also be asked to contact study personnel in the event of clinical deterioration (i.e., medical visit or hospitalization for pneumonia) or for any severe solicited events.

Study personnel will be available at each site for urgent issues related to the study or for communication with primary care providers who may have questions about the study.

Subjects who do not meet eligibility criteria or decline consent will be instructed to continue their initially prescribed antibiotic unless otherwise advised by their treating clinician.

7.3 Follow-up

Visit 2: Outcome Assessment Visit #1, Day 6-10

Subjects will be seen for a follow-up visit on Day 6-10. 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;
- The subject received non-study, systemic antibiotic therapy;
- The subject underwent drainage of pleural fluid, placement of a chest tube, or video assisted thoracoscopic surgery.

At the follow-up visit, study staff will complete the following procedures:

- Medical history to determine whether medically attended visits, receipt of non-study systemic antibiotics, or surgical procedures have occurred;
- Assessment of adequate clinical improvement as indicated by a parental report of lack of rectal, tympanic, axillary or oral temperature ≥38.3°C or 100.9°F, normalization of respiratory rate for age (<50 breaths/minute for children <24 months of age and <40 breaths/minute for children 24-71 months of age), and grading of cough.
- Physical assessment to determine vital signs (temperature, pulse and respiratory rates) and physical assessment (general appearance, hydration status, work of breathing, presence of skin rash);
- Review of the subject's memory aid to assess and record any solicited events and concomitant medications;
- Review of potential protocol-defined SAEs;
- Review of memory aid to assess treatment compliance;
- Collection of study product bottle for drug accountability, if available;
- Collection of a throat swab and stool specimen (if available), if consented for future use samples.

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 child 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 primary physician.

7.4 Final Study Visit

Visit 3: Outcome Assessment Visit #2, Day 19-25

Subjects will be seen for a follow-up visit on Day 19-25. 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 since the previous visit.

- The subject had a medically attended visit to an ED, urgent care, or clinic;
- The subject was hospitalized;
- The subject received non-study, systemic antibiotic therapy;
- The subject underwent drainage of pleural fluid, placement of a chest tube, or video assisted thoracoscopic surgery.

At the follow-up visit, study staff will complete the following procedures:

- Medical history to determine whether medically attended visits, receipt of non-study systemic antibiotics, or surgical procedures have occurred;
- Assessment of adequate clinical improvement as indicated by a parental report of lack of rectal, tympanic, axillary, or oral temperature ≥38.3°C or 100.9°F for >24 hours, normalization of respiratory rate for age (<50 breaths/minute for children <24 months of age and <40 breaths/minute for children 24-71 months of age), and grading of cough.
- Physical assessment to determine vital signs (temperature, pulse, and respiratory rate) and physical assessment (general appearance, hydration status, work of breathing, presence of skin rash);
- Review of the subject's memory aid to assess and record any solicited events and concomitant medications;
- Review of potential protocol-defined SAEs
- Review of memory aid assess treatment compliance (if not reviewed at Visit 2);
- Collection of study product bottle for drug accountability, if not collected at Visit 2 and if available
- Collection of a throat swab and stool specimen (if available), if consented for future use samples.

If the subject develops signs or symptoms of pneumonia (including fever, increased work of breathing, or increased cough) or develops a severe solicited event, the child 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 primary physician.

7.5 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 outcome assessment visits except no throat swab or stool specimen (if consented to participate in the collection of future use samples) will be collected. Unless they expressly state that they wish to have no additional

follow-up or data collection, subjects who withdraw from the study will receive a follow-up phone call approximately one week after their withdrawal. Study staff will review the memory aid and determine if any follow-up medical care was sought.

If the subject presents with symptoms such as fever and/or elevated respiratory rate at the Early Termination visit, the study team will inform the subject's PCP/pediatrician and will urge the parent(s) to follow-up with their primary provider.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

A screening medical history will be obtained by interview of subject's parents/caregivers during the prescreening telephone call and will be confirmed at the time of enrollment. Parent(s)/guardian(s) will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, or other chronic medical conditions will be obtained. 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.

Medication history (concomitant medications) will include a review of all current medications and medications taken within 30 days prior to signing the informed consent form through the last study visit. All 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 the enrollment visit, a physical assessment to assess eligibility will occur, which will include vital signs (temperature, pulse and respiratory rates); hydration status; an assessment of work of breathing; and presence of skin rash. If indicated based on subject's medical history or physical assessment, a more complete physical examination (conducted by a study clinician licensed to make medical diagnoses and listed as an investigator on the Form FDA 1572) may occur. An initial assessment of clinical response will be obtained to include maximum temperature in the past 24 hours and an assessment of improved activity and appetite since initiating antibiotic therapy.

An assessment of clinical response will occur at each follow-up visit. The assessment will include parental documentation of maximum temperature in the preceding 24 hours; normalization of respiratory rate; presence and extent of cough; occurrence of medically attended visits including visits to the ED, primary care physician, and urgent care; hospitalizations; use of non-study systemic antibiotics (parenteral or oral); and occurrence of surgical procedures. Vital signs (temperature, pulse and respiratory rates) will be collected at the enrollment visit and at each follow-up visit.

Solicited event assessments will include an assessment of solicited events occurring from the time of enrollment through the last visit, Visit 3. All subjects will complete a subject memory aid from the time of enrollment through Visit 3. Subject memory aids will be reviewed with the subject's parents for any discrepancies or missing data and will be returned to the subject's parent(s).

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

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

8.2.2 Special Assays or Procedures

N/A

8.2.3 Specimen Preparation, Handling, and Shipping

N/A

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

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

If the subject's parent/legal guardian consents to future use, clinical site personnel will obtain throat swabs and arrange collection of stool samples. Routine throat swabs will be obtained by site personnel at the time of enrollment, Outcome Assessment Visit #1, and Outcome Assessment Visit #2. Please refer to the MOP for specific details regarding type of swab. At enrollment, parents will be provided with a stool collection kit and instructions for sample collection. Parents will collect a stool sample within 24 hours after the enrollment visit and within 24 hours prior to Outcome Assessment Visits #1 and #2. Parents will be instructed to immediately store the stool sample in their home freezer. Parents will be instructed to bring the stool samples to the clinical site or sites will arrange pickup (e.g., courier services) at the subject's home. Samples will be transported to the laboratory in a freezer pack; once at the laboratory, samples will be stored at approximately -20°C, with temporary excursions up to -5˚C allowable. The microbial community composition has been shown to remain consistent in fecal samples stored at room temperature for up to 24 hours and for up to 14 days at 4°C or -20°C.[9,10] Moreover, samples are stable for up to 6 months at -80°C.[9,10]

Throat Swabs

Samples will be stored locally in an approximately 4˚C refrigerator, with temporary excursions up to 8˚C allowable, for up to 48 hours after collection. Samples will then be held in a -20˚C freezer (with temporary excursions to -5˚C allowable) until they are batch shipped to the DMID Clinical Agents Repository (CAR).

Stool Samples

Stool specimens will be obtained at Visits 1, 2, and 3. Specimens will be collected by retention of a fecal containing diaper or by collection of stool into a sterile cup that will be provided to the subject's parent/legal guardian. Samples can be collected within 24 hours of the study visit and maintained in a freezer in the subject's home until sent by courier or collected by study staff and transported to the study site. A minimum of approximately 2 teaspoons of stool will be collected. Samples will be stored locally and shipped according to Section 8.2.3.2.

8.2.3.2 Specimen Shipment

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

All specimens will be transported or shipped via courier under controlled conditions to the site (if collected at a home visit or affiliated clinic) and stored according to the MOP in order to maintain appropriate storage temperatures. When requested, samples will be batch-shipped to the DMID CAR per instructions in the MOP.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Amoxicillin, amoxicillin-clavulanate, cefdinir are approved drugs with established and well-described safety profile. The most prevalent of the drug side effects include:

Amoxicillin: Common side effects include rash, diarrhea, nausea, vomiting, and mucocutaneous candidiasis. Rare side effects include:

- Cardiovascular: hypersensitivity angiitis
- Central nervous system: agitation, anxiety, behavioral changes, confusion, dizziness, headache, hyperactivity (reversible), insomnia, seizure
- Dermatologic: acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Gastrointestinal: dental discoloration (brown, yellow, or gray; rare), hemorrhagic colitis, melanoglossia, pseudomembranous colitis
- Genitourinary: crystalluria
- Hematologic & oncologic: agranulocytosis, anemia, eosinophilia, hemolytic anemia, leukopenia, thrombocytopenia, thrombocytopenic purpura
- Hepatic: cholestatic hepatitis, cholestatic jaundice, hepatitis (acute cytolytic), increased hepative enzymes
- Hypersensitivity: anaphylaxis
- Immunologic: serum sickness-like reaction

Amoxicillin-clavulanate (in addition to side effects listed for amoxicillin above): Common side effects include diaper rash, abdominal discomfort, and loose stools. Other reported side effects include:

- Dermatologic: diaper rash, urticaria
- Gastrointestinal: abdominal distress, diarrhea, loose stools, nausea, vomiting
- Genitourinary: vaginitis
- Infection: candidiasis, vaginal mycosis
- Rare but important or life-threatening: cholestatic jaundice, headache, hepatotoxicity (idiosyncratic), increased liver enzymes, increased serum alkaline phosphatase, prolonged prothrombin time, thrombocythemia, vasculitis (hypersensitivity)

Cefdinir: Common side effects include rash, abdominal pain, nausea, vomiting, diarrhea, headache, and mucocutaneous candidiasis. Other side effects include:

- Central nervous system: headache
- Endocrine & metabolic: decreased serum bicarbonate, glycosuria, hyperglycemia, hyperphosphatemia, increased gamma-glutamyl transferase, increased lactate dehydrogenase
- Genitourinary: Proteinuria, occult blood in urine, urine alkalinization
- Hematologic: eosinophilia, lymphocytopenia, lymphocytosis, thrombocythemia, anemia

- Hepatic: increased serum alkaline phosphatase, increased serum ALT
- Rare but important or life-threatening: anaphylaxis, anorexia, blood coagulation disorder, bloody diarrhea, cholestasis, conjunctivitis, erythema multiforme, erythema nodosum, fulminant hepatitis, hemolytic anemia, hepatitis (acute), interstitial pneumonitis (idiopathic), pseudomembranous colitis, renal failure (acute), and Stevens-Johnson syndrome

As amoxicillin, amoxicillin-clavulanate, cefdinir are approved drugs with long prescribing history, NIAID does not expect that any new drug related safety signal will be detected in this trial. As such, the safety data collection will be targeted to only collect protocol defined SAEs and Suspected Unexpected Serious Adverse Reaction (SUSAR, See Section 9.2.2).

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

9.2.1 Adverse Events

Adverse Event (AE): International Conference 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.

As the safety profile of amoxicillin, amoxicillin-clavulanate, and cefdinir are well established, and this trial is not powered to detect new, unknown safety signals, **there will be no unsolicited AE collection during this study and only protocol-defined SAE's will be collected**.

9.2.1 Solicited Adverse Events

Solicited adverse events that are common and known to occur following administration of the study product. Solicited adverse events will be recorded daily for the duration of the study. The following grading scale will be used to grade solicited adverse events:

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Irritability	More irritable or fussy than usual but can be consoled; no interference with smiling/playing	Irritability or fussiness that is difficult to console and interferes with smiling and playing	Irritability or fussiness that lasts for more than 4 consecutive hours in a 24 hour period or cannot be consoled
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 occurring >6 times/day	Bloody diarrhea, or diarrhea that requires medical intervention, laboratory testing, or hospitalization

Allergic Reaction	Localized rash or pruritus without rash	Diffuse rash (maculopapular or urticarial)	Generalized rash consistent with Stevens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis; anaphylaxis; or angioedema
Stomatitis	Oral lesions associated with parenteral report of mild oral discomfort	Oral lesions associated with difficulty swallowing, but able to eat and drink	Oral lesions associated with inability to swallow solids or liquids; requires medical intervention, IV fluids, or hospitalization
Candidiasis	Mild mucocutaneous candidiasis or diaper dermatitis, with no treatment or topical treatment only	Moderate mucocutaneous candidiasis requiring oral antimicrobial treatment	Severe mucocutaneous candidiasis; requires medical intervention, intravenous treatment, or hospitalization

In addition to the solicited adverse events specified above, the presence and severity of cough will be recorded daily for the duration of the study to allow for assessment of the resolution of pneumonia symptoms. The following grading scale will be used to grade cough

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Cough	Occasional coughing (less than 4 times hourly)	frequent coughing (4 or more times an hour], interferes with sleep)	Almost constant coughing (never free of cough), makes sleep nearly impossible

9.2.2 Serious Adverse Events

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event[1],
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[1] Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, might have caused death.

Protocol defined SAEs: For this protocol, only the following SAEs will be collected, regardless of the relationship to study drug.

- Death that is not the result of trauma or accident
- Anaphylaxis
- Laryngospasm or bronchospasm within 1 day after initiation of the study treatment
- Stevens-Johnson syndrome
- Severe erythema multiforme
- Toxic epidermal necrolysis

SAEs must be graded for severity and assessed for relationship to study product (see definitions below).

Severity of Event: SAEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.

- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.

- Severe (Grade 3): Events interrupt the subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Relationship to Study Product: The study physician's assessment of an SAE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in this study. If there is any doubt as to whether a clinical observation is an SAE, the event should be reported. The relationship to study product must be assessed for SAEs using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.3 Procedures to be Followed in the Event of Abnormal Clinical Findings

Subjects will be evaluated for the adequacy of clinical response and for the occurrence of solicited events at the outcome assessment visits. If a serious adverse event is suspected, or if clinical response is inadequate, subjects will be referred immediately to their primary provider or local ED/urgent care.

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

All SAEs will be:

- Assessed for severity and causal relationship by a physician listed on the Form FDA 1572 as the principal investigator (PI) or sub-investigator.
- Recorded on the appropriate SAE report form.
- Followed through resolution by a study physician.
- Reviewed by the safety monitor, the SMC (periodic review unless associated), DMID Medical Monitor, and the local IRB.

Death, life-threatening events, hospitalization or prolongation of existing hospitalization, and other important medical events are part of the efficacy endpoints of this trial and will not be reported or collected as SAEs, unless meeting the SAE reporting criteria included in Section 9.2.2.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20814, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, selected SAE data fields must also be entered into the Emmes AdvantageEDC web-based data entry system. Refer to the Manual of Procedures for details regarding this procedure. Timelines for submission of an SAE form are as follows:

- All non-accidental deaths and life-threatening events, regardless of relationship, will be recorded on the SAE form and sent by fax within 24 hours of site awareness of the death or event.
- All other SAEs, regardless of relationship, will be reported via fax by the site within 24 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the subject to be stable.

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site principal investigator or appropriate sub-investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating site principal investigators (i.e., all principal investigators to whom the sponsor is providing drug under its IND(s) or under any principal investigator's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Study related solicited events will be followed until resolution 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, 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 2 subjects (or >2% if more than 100 subjects enrolled) that requires intensive care or leads to death due to persistent/worsening pneumonia
- More than five subjects (>5% if more than 100 subjects enrolled) experience persistent/worsening pneumonia within 3 days of initiation of study treatment
    - Persistent/worsening pneumonia is a clinical diagnosis, accompanied by the following clinical characteristics:
        - administration of non-study directed systemic antibiotic therapy, hospitalization, or surgical intervention (e.g., placement of a chest tube) for persistent/worsening pneumonia
- More than 2 subjects (>2% if more than 100 subjects enrolled) experience an SAE of laryngospasm, bronchospasm, or anaphylaxis within 1 day after initiation of study treatment that is suspected to be related to study product.

- More than 2 subjects (>2% if more than 100 subjects enrolled) experience death (that is not the result of trauma or accident) within 3 days of initiation of study treatment and is suspected to be related to study product.

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
- 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.

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 participant, 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 participant, clinical, and safety data that may include enrollment and demographic information, medical history, concomitant medications, physical assessments, dosing, solicited events, and SAEs. 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. The DMID Medical Monitor will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during the study.

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 any issues noted

In this protocol, a ‘specific site’ is defined as one in which resources for the study (e.g., study staff, storage facilities, drug storage, or study records) are housed. Monitoring visits will focus on these specific sites to ensure compliance with DMID and ICH/GCP policies, procedures, and guidelines. In addition, a significant number of visits will occur in non-site locations, such as community clinics or home visits. These ‘generic’ sites will not be considered part of the site monitoring plan.

11 STATISTICAL CONSIDERATIONS

This is a randomized double-blinded placebo-controlled trial comparing a strategy of short course (5-days) vs. standard course (10-days) oral beta-lactam antibiotic therapy with respect to desirability of outcome in children with CAP.

The trial is designed using Response Adjusted for Days of Antibiotic Risk (RADAR).[11] RADAR utilizes a superiority trial design under the conceptual framework, evaluating whether a strategy of short course antibiotic therapy is better than the standard course strategy when considering the totality of all of the important outcomes (adequacy of the clinical response, adverse events, and the duration of antibiotic use).

All trial participants are assigned a desirability of outcome ranking (DOOR), constructed as follows:

I. Each subject is evaluated according to the ordinal clinical response (Refer to Section 3.2.1)

II. DOOR is assigned according to two rules:

(i) When comparing two subjects with different ordinal clinical responses, the subject with a better ordinal clinical response receives a higher rank.

(ii) When comparing two subjects with the same ordinal clinical response, the subject with fewer days of antibiotic use receives a higher rank. Days of antibiotic use are defined as the number of days for which the subject is reported to have taken at least one dose of non-placebo study product or a non-study product systemic antibiotic.

During analyses, the distributions of DOORs are compared between short-course and standard-course strategies. The sum of the probability that a randomly selected participant from the short course strategy will have a better DOOR than a randomly selected participant from the standard course strategy plus one-half the probability that the DOORs are equal is estimated using a confidence interval.

The primary outcome measure is the DOOR at Outcome Assessment Visit #1 (defined above). DOOR at Outcome Assessment Visit #1 is computed using data from Day 1 to Day 5.

Secondary outcome measures include:

1. DOOR at Outcome Assessment Visit #2. DOOR at Outcome Assessment Visit #2 is computed using data from Day 1 to Day 18
2. Adequate clinical response rates (a component of DOOR) at each outcome assessment visit, defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
3. Resolution of symptoms (a component of DOOR) at each outcome assessment visit, defined as the absence of fever, tachypnea, or cough of Grade 2 or higher.

4. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for persistent or worsening pneumonia at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.
5. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for all causes at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.

Exploratory outcome measures include:

1. DOOR at Outcome Assessment Visits #1 and #2, when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

11.1 Study Hypothesis

- Null: the sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

11.2 Sample Size Considerations

The primary study sample size is based on a superiority test of the null hypothesis in 11.1, under an assumed alternative hypothesis that the sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 60% (p=60%).

A sample size of 360 (180 per arm) provides 90% power using a 2-sided alpha=0.05 with a Wilcoxon Mann-Whitney U test. If p=65% or 70%, then a total sample size of 160 (80 per arm) or 90 (45 per arm), respectively, would be required. The sample size is inflated by ~10% based on an estimate from a similar study, in order to account for loss to follow-up resulting in a total sample size of 400 (200/arm).

11.3 Planned Interim Analyses

11.3.1 Safety Review

A Data Safety Monitoring Board (DSMB) appointed by NIAID will monitor this protocol. Interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical assessments, dosing, and protocol specific SAEs and SUSAR. 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 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 the study or to modify or terminate the study.

Additionally, the study will be monitored to determine if any of the halting rules described in Section 9.5 are met.

11.3.1 Interim Analysis of Efficacy, Futility, and Safety

One interim analysis, described below, will be performed and reported to the DSMB after approximately 30% of the targeted subjects have completed the study. The interim analysis will inform DSMB decisions regarding stopping early for efficacy, futility, or safety.

For the interim analysis, a snapshot of the study database will be unblinded and used to conduct analyses as follows. An ITT analysis including all enrolled subjects in the snapshot of the study database will be performed, testing the null hypothesis provided in Section 11.1 using the methods described in Section 11.4.1, with the modification that the Haybittle-Peto boundary ($p<0.001$) will be used when concluding statistical significance. The study may be stopped early for efficacy only if statistical significance is detected in that test. In the event of statistical significance, sensitivity analyses using complete case and according-to-protocol cohorts (CC-V1 and ATP-V1, as described below) as well as worst case analyses will be included in the DSMB report to further guide decisions for stopping for efficacy.

A 95% confidence interval for the probability that a randomly selected subject will have a better DOOR if assigned to the 5-day strategy (vs. the standard strategy) will be estimated but not used to inform DSMB decisions about stopping early for efficacy. Predicted interval plots (PIPS)[12,13] will be constructed to provide the DSMB with a prediction of the trial results were the trial to continue as planned under varying assumptions regarding future data (e.g., current trend continues, null hypothesis is true, alternative hypothesis is true).

The DSMB will also be provided with the following:

1. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a between arm difference in the overall outcome (DOOR) via a cumulative difference plot with respective confidence bands for Outcome Assessment Visit #1

2. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics at Outcome Assessment Visit #1.

3. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) Oral, rectal, axillary or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding Outcome Assessment Visit #1, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia; (2) Elevated respiratory rate (RR >50

breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at Outcome Assessment Visit #1, and (3) Presence of cough Grade 2 or 3 at Outcome Assessment Visit #1.

4. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of each solicited event and with the risk difference of any solicited event, for each severity threshold (mild or greater, moderate or greater, or severe) for Outcome Assessment Visit #1.

11.4 Final Analysis Plan

The primary analysis of the primary endpoint will be performed according to an intention-to-treat (ITT) approach and include all randomized subjects. As (secondary) sensitivity analyses of the primary endpoint, complete case analyses using the CC-V1 / ATP-V1 cohorts (defined below) and a worst case analysis using the ITT cohort of the primary endpoint will be performed.

Intention-to-Treat Cohort: All randomized participants, analyzed as randomized. Subjects that have not received at least one dose of study product will have adequate clinical response and its sub-components treated as missing.

Complete Case Cohorts (CC): Subjects in a CC analysis are analyzed as randomized, but excluded from analysis if missing data prevents assigning an unambiguous value to the DOOR endpoint or if the subject has not received at least one dose of study product. The CC-V1 cohort will consist of all subjects with sufficient data to define unambiguously the Visit #1 DOOR. The CC-V2 cohort will consist of all subjects with sufficient data to define unambiguously the Visit #2 DOOR.

According-to-Protocol Cohorts (ATP): Subjects in an ATP analysis require at least one dose of study product each day from Day 1 to Day 5 and furthermore subjects will excluded from analysis if missing data prevents assigning an unambiguous value to the DOOR endpoint The ATP-V1 cohort will restrict subjects to those with sufficient data to define unambiguously the Visit #1 DOOR. The ATP-V2 cohort will restrict subjects to those with sufficient data to define unambiguously the Visit #2 DOOR.

Details of what constitutes sufficient data to assign an unambiguous value to DOOR will be specified in the statistical analysis plan.

11.4.1 Primary Analysis

For the primary analyses, the DOORs will be compared between the 5- and 10-day arms. The sum of the probability that a randomly selected subject will have a better DOOR if assigned to the 5-day arm for Outcome Assessment Visit #1 plus one-half the probability of equal DOORs for Outcome Assessment Visit #1 will be estimated. The null hypothesis to be tested is that the probability is equal to 0.50 (lack of superiority of short-course therapy). The primary analysis will be carried out using the ITT cohort, with missing DOOR values (treated as continuous) imputed using multiple imputation, utilizing linear regression models corresponding to relevant observed data (baseline covariates and observed DOOR components from an early termination

visit, if available). The Mann-Whitney U statistic will be combined across the datasets to give the test statistic and Rubin's Rules used to define distribution of the test statistic under the null hypothesis. The test of the null hypothesis will be two-sided with a Type I error of 0.05. A point estimate of the estimand will be computed by dividing combined test statistic by the number of pairwise comparisons and a confidence interval of the estimand will be computed by inverting the described test of the null hypothesis.

11.4.2 Secondary Analyses

All secondary and exploratory analyses will use a Type I error rate of 0.05 and will not correct for multiple comparisons. All tests will be two-sided.

Secondary analyses will include:

- Analysis of DOOR at Outcome Assessment Visit #2, performed as ITT in an analogous manner to the primary analysis.

- Sensitivity Analyses for the DOOR at Outcome Assessment Visits #1 and #2 ITT analyses. (1) CC analyses. (2) ATP analyses. (3) Worst case analyses: all imputations of missing data will be the worst case (result in the lowest possible DOOR given available information) for subjects in the 5-day arm and best case for subjects in the 10-day arm. Sensitivity analyses will test the null hypothesis using the Mann-Whitney U Test, estimate using U divided by the number of pairwise comparisons, and will compute confidence intervals by (1) inverting the Mann-Whitney U Test and (2) using a non-parametric bootstrap.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of each solicited event and the risk difference of <u>any</u> solicited, for each severity threshold (mild or greater, moderate or greater, or severe). Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) Oral, rectal, axillary or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding the Outcome Assessment Visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia; (2) Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit; and (3) Presence of cough Grade 2 or 3 at the Outcome Assessment Visit. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions <u>for persistent or worsening pneumonia:</u> (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics. Tests

for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for all causes: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Analysis of the ordinal clinical response at Outcome Assessment Visits #1 and #2. The ITT analysis will treat the ordinal clinical response as Normal distributed and use multiple imputation to compute confidence intervals for the mean ordinal clinical response by treatment assignment and to test whether the mean ordinal clinical response varies by treatment assignment. CC, ATP, and worst case analyses of the ordinal clinical response will be performed; separately for Outcome Assessment Visit #1 and #2, a cumulative difference plot with respective 95% confidence bands for the ordinal clinical response (and an associated result from a Mantel-Hantzel chi-square test on the ordinal clinical response) will be computed. Non-inferiority analyses of the ordinal clinical response at Outcome Assessment Visits #1 and #2 using the ITT cohort, to be specified in the statistical analysis plan, may be carried out.

11.4.3 Exploratory Analyses

Increased RADAR thresholds sensitivity analysis. In the primary RADAR/DOOR analysis, if two subjects from separate treatment arms have an equal ordinal clinical response but a difference in the duration of antibiotic use of at least $k = 1$ day, RADAR assigns a more favorable response to the subject with fewer days of antibiotic use. For a sensitivity analysis, the effect of increasing the minimum difference in the duration of antibiotic use ($k = 2,3,4,$ or 5) before a favorable response is given to the subject with shorter duration of antibiotic use will be explored. For each value of k, bootstrapped confidence intervals of the probability of more favorable DOOR due to assignment to the 5-day antibiotic course will be computed and plotted versus k. Analysis will be performed separately for DOOR at Outcome Assessment Visit #1 and DOOR at Outcome Assessment Visit #2. Analyses will be performed using CC-V1/CC-V2 cohorts.

Other exploratory analyses, if required, to be specified in the statistical analysis plan.

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 ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate 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. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or 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 trial. Data collection forms will be derived from the eCRFs and be provided by the Statistical and Data Coordinating Center (SDCC).

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating VTEU sites and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The 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. The 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 beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

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.

14.3 Informed Consent Process

14.3.1 Informed Consent

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.

Local IRB requirements will govern subject recruitment efforts and pre-enrollment 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.

14.3.2 Informed Consent/Assent Process (in Case of a Minor)

Parents or legal guardians will be asked to provide consent for the participation of their children as outlined in Section 14.3.1. Since all eligible children in this study are <7 years of age, formal written assent will not be obtained; nevertheless, study personnel will explain the study to the child in age appropriate terms and will ensure that the well being of participating children is protected.

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

This study is focused on children age 6-71 months of age and will include 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. If a written contract for the conduct of the trial which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

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 Future Use of Stored Specimens

Subjects will be asked for permission to keep any samples for use in future research studies, such as analyzing the impact of antibiotic usage of the microbiome. Some samples may be stored at the local site and some at a central clinical storage facility. Samples may be shared with other investigators at other institutions, provided that appropriate human subject protection plans are in place. The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on samples. 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 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, 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 statistical reports may be generated as deemed necessary and appropriate by DMID. Safety and efficacy summary reports may be generated for the DSMB.

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 for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified. 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

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

17 LITERATURE REFERENCES

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13 Li, L., Evans, S., Uno, H. & Wei, L. A graphical tool for data monitoring in clinical trials. *Statistical Biopharmaceutical Research* (2009).

APPENDIX A – Schedule of Evaluations

	Initial treatment of CAP and Eligibility Screening[1]	Enrollment Visit	Receipt of Study Agent[2]	Outcome Assessment Visit #1	Outcome Assessment Visit #2	Early Termination Visit (as applicable)
Visit Number		1		2	3	
Visit Day	Days -5 to 1	Day -3 to -1	Days 1-5	Day 6-10	Day 19-25	
Screening and Enrollment						
Initially prescribed antibiotic therapy	X					
Review of electronic medical records to assess eligibility[3]	X					
Phone contact with parent/guardian to assess eligibility	X					
Obtain Informed Consent		X				
Review Eligibility Criteria		X				
Medical History[4]		X		X	X	X
Concomitant Medications		X		X	X	X
Vital Signs (temperature, pulse, respiratory rate)		X		X	X	X
Physical Assessment[5]		X		X	X	X
Assess clinical response to initial antibiotic therapy		X				
Enrollment and Randomization		X				
Dispense study agent[2]		X				
Distribute Memory Aid and Study-Related Materials		X				
Follow-up						
Receipt of study agent			X			
Collection of study product bottle				X	X[7]	X[7]
Review of electronic medical record to assess clinical response[6]				X	X	X
Review Memory Aid				X	X	X
Assess clinical response to therapy				X	X	X
Assess solicited events				X	X	X
Collection of Future Use Samples (if consented)						
Throat Swab		X		X	X	
Collection of stool		X		X	X	

Footnotes:

1. Day -5 is defined as the date on which the diagnosis of CAP is made and treatment with oral beta-lactam therapy is initiated.
2. Study drug will be either a continued course of the oral antibiotic therapy that was initially prescribed (oral amoxicillin, amoxicillin-clavulanate, or cefdinir) or a 5 day course of matching placebo, which will begin on Day 1.
3. Electronic medical records will be used to preliminarily assess eligibility, including: age of the subject; diagnosis of CAP (a diagnosis of "pneumonia" is sufficient) without additional diagnoses of bronchiolitis or croup; initial antibiotic therapy for CAP with sufficient dose (i.e., prescription of amoxicillin or amoxicillin/clavulanate with an amoxicillin dose of 80-100 mg/kg/day or prescription of cefdinir of 12-16 mg/kg/day); absence prescription of any other antibiotic therapy ≤7 days before the diagnosis of CAP; absence of initial antibiotic therapy for CAP with combination therapy (i.e., amoxicillin, amoxicillin/clavulanate or cefdinir plus one or more additional antibiotics), with the exception of 1 dose of intravenous or intramuscular cefotaxime or ceftriaxone as noted in the subject inclusion criteria; absence of a history of allergy to amoxicillin or oral cephalosporin antibiotics (except cefaclor); absence of radiographic findings of complicated pneumonia (pleural effusion, lung abscess, or pneumatocele) on the initial chest radiograph (if obtained) or any subsequent chest radiograph; absence of hospitalization for pneumonia during day 1-5 of antibiotic therapy for CAP; absence of blood or pleural fluid culture positive for *S. aureus* or group a streptococcus; absence of history of other conditions as described on the exclusion criteria; any other condition that in the judgment of the investigator precludes participation because it could affect the safety of the subject; current participation in any other clinical trial.
4. Medical history will include acute or chronic medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency and autoimmune disease will be solicited. The history will include capture of sociodemographic data.
5. A physical assessment will be performed to determine general appearance and hydration status; vital signs, including temperature, pulse, and respiratory rate; an assessment of work of breathing, and presence of skin rash. This can be performed by a nurse, advanced practice nurse, physician assistant, pr physician.
6. Study staff will make a preliminary EHR-based assessment of clinical response to determine whether any of the following events occurred after initiation of study drug: a medically attended visit to an ED or outpatient clinic; receipt of non-study antibiotic [parenteral or oral]; treatment for a local pneumonia complication, including drainage of pleural fluid, placement of a chest tube, or video assisted thoracoscopic surgery.
7. If not collected at previous visit.

A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)

DMID PROTOCOL NUMBER: 14-0079

DMID FUNDING MECHANISM: VACCINE AND TREATMENT EVALUATION UNIT

IND SPONSOR: NIH/NIAID/DMID

VTEU PRINCIPAL INVESTIGATOR: C. BUDDY CREECH, MD, MPH

ARLG PRINCIPAL INVESTIGATORS: W. CHARLES HUSKINS, MD, MSC

& THEOKLIS ZAOUKIS, MD, MCSE

VERSION NUMBER: 4.0

14 DECEMBER 2018

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 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- 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 United States of America (US) federal regulations and ICH guidelines.

_____

Site Principal Investigator Signature

Date: _____

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LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ARLG	Antibiotic Resistance Leadership Group
ATP	According-to-Protocol
CAP	Community Acquired Pneumonia
CC	Complete Case
CFR	Code of Federal Regulations
CMS	Clinical Materials Services
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOOR	Desirability of Outcome Ranking
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EHR	Electronic Health Record
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDES	Internet Data Entry System
IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-to-Treat
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RADAR	Response Adjusted for Days of Antibiotic Risk
SAE	Serious Adverse Event/Serious Adverse Experience
SDCC	Statistical and Data Coordinating Center
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
USP	United States Pharmacopeia

PROTOCOL SUMMARY

Title:	A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)
Phase:	IV
Population:	Approximately 400 subjects aged 6-71 months of age with community acquired pneumonia (CAP)
Description of Sites/Facilities Enrolling Participants:	5 to 10 US outpatient sites
Study Duration:	25 months
Subject Participation Duration:	~1 month after beginning antibiotic therapy
Description of Agent or Intervention:	Oral suspensions of amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos
Objectives:	**Primary:** 1. To compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs. standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days) **Secondary:** 1. To compare the composite overall outcome (DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #2 (Study Day 22 +/- 3 days) 2. To compare the resolution of symptoms (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2

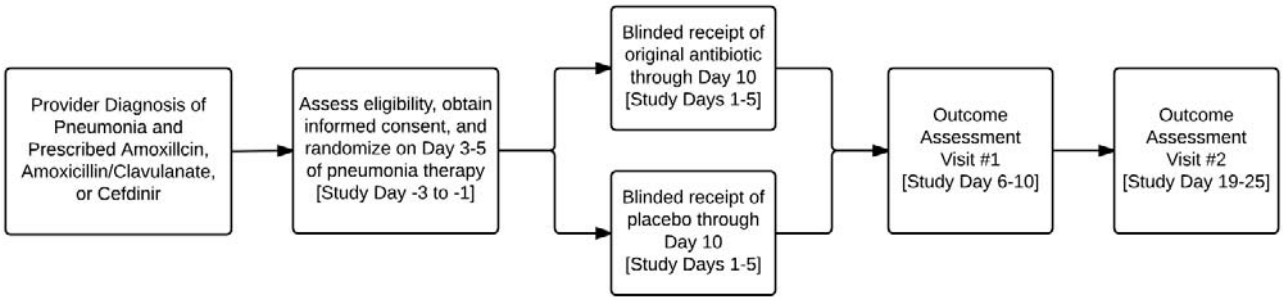
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
4. To compare solicited events (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
5. To compare medically attended visits to Emergency Departments (ED) or outpatient clinics, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics (components of the clinical response) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2

Exploratory:

1. To examine the robustness of results of DOOR comparisons when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

Description of Study Design:	Double-Blind, Placebo-Controlled, Randomized Trial
Estimated Time to Complete Enrollment:	Approximately 24 months

Figure 1:Study Schematic



1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The World Health Organization estimates 156 million cases of pneumonia occur annually in children <5 years of age.[1] In the United States (US), an estimated 1.5 million ambulatory visits for community-acquired pneumonia (CAP) in children occur annually.[2] Hospitalizations for CAP in children have decreased after the introduction of pneumococcal conjugate vaccine.[3] Further, in a pneumonia etiology study of >2500 children hospitalized with CAP in 3 US cities between 2010 and 2012, viral pathogens accounted for >70% of detections, while bacteria were identified in <20%.[4] However, ambulatory visits have not decreased, and pediatric CAP remains a very common infection for which antibiotics are generally prescribed.[2]

A 2011 Infectious Diseases Society of America (IDSA) guideline for management of CAP in children provides recommendations for antibiotic therapy.[5] Regarding the treatment duration for beta-lactam antibiotics, the guideline states “courses of 10 days have been best studied.” Two studies conducted in resource-poor settings found no difference in outcomes between 3 vs. 5 days of oral therapy or 3 days of oral therapy vs. placebo for non-severe pneumonia.[6,7] However, these studies likely included many subjects with viral infection because substantial proportions had no radiographic findings or included children with wheezing. While stating “shorter courses may be just as effective,” the IDSA guideline concluded there was insufficient evidence to recommend short course therapy.[5] The guideline identified clinical trials that provide information on the “shortest duration of therapy to decrease the development of antimicrobial resistance and the risk of antimicrobial toxicity” as a priority for future research.[5]

2.2 Rationale

In 2014, a randomized trial of short vs. standard course therapy in young children in Israel with CAP suspected to be of bacterial origin found a higher rate of treatment failure (40%) in subjects treated for only 3 days vs. subjects treated for 5 or 10 days.[8] The study was underpowered to detect a difference in treatment failure between subjects treated for 5 vs. 10 days, but treatment failure did not occur in either group.

The proposed study will test the effectiveness of short (5-day) vs. standard (10-day) course therapy in children who are diagnosed with CAP and initially treated in outpatient clinics, urgent care facilities, and emergency departments. The study will specifically address whether short course therapy is superior to standard therapy among children that have clinically improved since diagnosis. If superior to standard course therapy, short course therapy could reduce antibiotic exposure among young children. We will use a study methodology similar to the SCOUT Study (“Short Course Therapy for Urinary Tract Infections in Children”)—a randomized, double-blind, placebo-controlled non-inferiority trial of short course antimicrobial therapy for urinary tract infection in children sponsored by NIAID through the “Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance” initiative. However, the SCOUT-CAP trial will use a superiority study design using an ordinal composite overall outcome (Desirability of Outcome Ranking, DOOR, see 3.2.1 Primary Outcome Measures)—to test the hypothesis that short

course (5 day) therapy is superior to standard course (10-day) beta-lactam therapy in children who have experienced early clinical improvement of pneumonia.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The potential risk of short course therapy is that clinical outcomes may not be equivalent to standard course therapy. Specifically, the percent of children with adequate clinical response (or in this case, no relapse of illness) may be lower in children receiving short course therapy. Adequate clinical response can be defined as resolution or substantial improvement in clinical signs and symptoms (e.g., fever, cough, respiratory rate, work of breathing) and the lack of need for additional antibiotic therapy, additional contacts with the health care system, or surgical procedures for worsening pneumonia. The magnitude of this risk is not well established, although a study from Israel suggests it is small[8]; nevertheless, this degree of risk will be evaluated during this trial.

2.3.2 Known Potential Benefits

If, as assessed by the primary outcome, short course therapy is superior to standard course therapy, short course therapy will reduce antibiotic exposure among children with CAP. The potential benefits of reduced antimicrobial exposure involve benefits both to the individual child and the population as a whole.

Potential benefits to the individual child include a simpler course of therapy, a lower risk of an adverse event associated with antibiotic therapy (e.g., antibiotic associated diarrhea, *Clostridium difficile* infection) and a lower risk of becoming colonized with antibiotic resistant bacteria.

Potential benefits to the population include a lower prevalence of colonization with pathogenic antibiotic resistant bacteria among children treated for CAP. Since these bacteria are transmissible, a lower prevalence of colonization among children treated for CAP confers a potential lower risk of colonization among all persons in the population, including children and adults regardless of whether they are treated with antibiotics.

3 OBJECTIVES

3.1 Study Objectives

Primary:

1. To compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days)

Secondary:

1. To compare the composite overall outcome (DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #2 (Study Day 22 +/- 3 days)
2. To compare the resolution of symptoms (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
4. To compare solicited events (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
5. To compare medically attended visits to Emergency Departments (ED) or outpatient clinics, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics (components of the clinical response) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2

Exploratory:

1. To examine the robustness of results of DOOR comparisons when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The primary endpoint/outcome measure is the DOOR at Outcome Assessment Visit #1.

DOOR is defined as follows:

I. Each subject is evaluated according to the ordinal composite outcome (See Table 1 below) and assigned an outcome rank ranging from 1-8.
II. Desirability of Outcome Ranking (DOOR) is then assigned according to two rules:
   (i) When comparing two subjects with different ordinal responses, the subject with a better ordinal response receives a higher rank.
   (ii) When comparing two subjects with identical ordinal responses, the subject with fewer days of antibiotic use receives a higher rank.

The ordinal composite outcome involves an assessment of whether the subject has an adequate clinical response and whether they have experienced any solicited events as defined below.

Table 1. Ordinal Outcome

	Adequate clinical response[1] (Assessed at Outcome Assessment Visits #1 and #2)	**Solicited events[3] (Assessed at Outcome Assessment Visits #1 and #2)**
1	Yes, with resolution of symptoms[2]	None
2	Yes, with resolution of symptoms[2]	Mild (Grade 1)
3	Yes, with resolution of symptoms[2]	Moderate (Grade 2)
4	Yes, with resolution of symptoms[2]	Severe (Grade 3)
5	Yes, with persistent symptoms of fever, tachypnea, or cough	None or any grade
6	No, with ED/clinic visit but no hospitalization	None or any grade
7	No, with hospitalization	None or any grade
8	Death from any cause	

[1]Adequate clinical response is defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.

- Persistent or worsening pneumonia is defined as receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
- Note: Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

[2]Resolution of symptoms is defined as the absence of all of the following:

- Oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding the Outcome Assessment Visit or measured at the Outcome Assessment Visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia;
- Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit;
- Presence of cough grade 2 or 3 at the Outcome Assessment Visit, (defined in Table 2).

[3]Solicited events (Table 3) will be captured daily until Outcome Assessment Visit #2; thereafter, parents/legal guardians will report symptoms based on memory aid and medical interview by

study staff. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Table 2: Severity of Cough

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Cough	Occasional coughing (less than 4 times hourly)	Frequent coughing (4 or more times an hour], interferes with sleep)	Almost constant coughing (never free of cough), makes sleep nearly impossible

Table 3. Solicited Events Grading

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Irritability	More irritable or fussy than usual but can be consoled; no interference with smiling/playing	Irritability or fussiness that is difficult to console and interferes with smiling and playing	Irritability or fussiness that lasts for more than 4 consecutive hours in a 24 hour period or cannot be consoled
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 occurring >6 times/day	Bloody diarrhea, or diarrhea that requires medical intervention, laboratory testing, or hospitalization
Allergic Reaction	Localized rash or pruritus without rash	Diffuse rash (maculopapular or urticarial)	Generalized rash consistent with Stevens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis; anaphylaxis; or angioedema
Stomatitis	Oral lesions associated with parenteral report of mild oral discomfort	Oral lesions associated with difficulty swallowing, but able to eat and drink	Oral lesions associated with inability to swallow solids or liquids; requires medical intervention, IV fluids, or hospitalization
Candidiasis	Mild mucocutaneous candidiasis or diaper dermatitis, with no treatment or topical treatment only	Moderate mucocutaneous candidiasis requiring oral antimicrobial treatment	Severe mucocutaneous candidiasis; requires medical intervention, intravenous treatment, or hospitalization

3.2.2 Secondary Outcome Measures

Secondary outcome measures include:

1. DOOR at Outcome Assessment Visit #2.
2. Resolution of symptoms (a component of DOOR) at each outcome assessment visit, defined as the absence of fever, tachypnea, or cough of grade 2 or higher.

3. Adequate clinical response rates (a component of DOOR) at each outcome assessment visit, defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
4. Frequency of solicited events at each outcome assessment visit, as listed in Table 3.
5. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for persistent or worsening pneumonia (as defined above) at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.
6. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for all causes at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotic) will be compared between treatment groups.

3.2.3 Exploratory Outcome Measures

1. DOOR at Outcome Assessment Visits #1 and #2, when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

4 STUDY DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled, superiority clinical trial evaluating short course (5 day) vs. standard course (10 day) of oral beta-lactam antibiotic therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) for treatment of CAP in children 6-71 months of age who have clinically improved prior to enrollment. The study will randomize approximately 400 enrolled subjects to one of the two study arms (approximately 200 children in each arm) in order to reach 360 subjects completing Outcome Assessment Visit 1. Subjects will be randomized (1:1) to receive either a standard course of the initially prescribed antibiotic (10 days) or a short course of the initially prescribed antibiotic (5 days) plus 5 days of matching placebo.

The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Day -5 is defined as the date on which oral beta-lactam therapy is initiated for a diagnosis of CAP. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. These subjects will be assessed for eligibility and enrolled on Day -3 to -1 of their initially prescribed oral beta-lactam therapy. Subjects may also be enrolled on Day 1 (the first day of receipt of study agent) provided they have not yet received any doses of the healthcare provider-prescribed antibiotic therapy for that day.

A Schedule of Events is provided in Appendix A.

Visit 1: Enrollment Visit. Subjects who meet the eligibility criteria, and whose parent/guardian consents for participation in the study, will complete an Enrollment Visit on Day -3 to -1. Subjects satisfying the inclusion criteria with no exclusion criteria will be enrolled and randomized. Enrolled subjects will continue to receive the initially prescribed antibiotic through Day -1. The subjects' parents/guardians will be instructed to contact study personnel if their child develops fever or worsening respiratory symptoms (worsening cough, increased work of breathing, any other concerning symptoms in the parents' estimation) following enrollment.

Randomization: Enrolled subjects will be randomized to short vs. standard course therapy at a 1:1 ratio, with stratification by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility).

Intervention: Subjects will continue on the initially prescribed antibiotic through Day -1, until they have completed 5 days (i.e., 5 scheduled doses of once daily medication, 10 scheduled doses of twice daily medication) of antibiotic therapy [e.g., if a subject takes the first dose of antibiotic in the afternoon of Day -5, the first dose of study agent would occur on the afternoon of Day 1, providing 10 total scheduled doses of a twice daily prescribed antimicrobial]. The first day of receipt of study agent will be Day 1. Subjects assigned to standard course therapy will receive 5 additional days (10 doses) of the same initially prescribed antibiotic, with standardized twice-daily dosing. Subjects assigned to short course therapy will receive 5 more days (10 doses) of a matching placebo. Both the study agent and placebo may appear different than the commercial formulation the child originally received. The placebo will appear indistinguishable in

color, taste, thickness, and consistency as the active antibiotic the child would otherwise receive in the study. The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation.

Follow-up and Assessment of Endpoints: Subjects will be scheduled for the following assessment visits:

Visit 2: Outcome Assessment Visit #1, Day 6 to 10 (1-5 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Visit 3: Outcome Assessment Visit #2, Day 19 to 25 (14-20 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects who are identified as having an inadequate clinical response prior to Outcome Assessment Visit #1 will be asked to complete Outcome Assessment Visits #1 and #2 in order to evaluate the occurrence of any solicited events and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects will be invited to contribute oropharyngeal and stool specimens at specified times throughout the study for future use (see Appendix A, Schedule of Events). Additional informed consent will be obtained for future use sample collection.

5 STUDY ENROLLMENT AND WITHDRAWAL

Subjects who are diagnosed with CAP in EDs, urgent care facilities, and clinics will be screened for eligibility. Screening will continue until 400 subjects are enrolled cumulatively across all the study sites. The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on antibiotic therapy using oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. Other forms and/or mechanisms of recruitment may also be used. The local IRB will approve recruitment materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

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

Eligible subjects may be included in the study if they meet ALL of the following criteria at the Enrollment Visit (Day -3 to -1):

1. Age 6 – 71 months
2. Provider diagnosis of CAP and prescription of antibiotic therapy with amoxicillin[1], amoxicillin-clavulanate[1], or cefdinir[2]

   [1] amoxicillin or amoxicillin-clavulanate prescribed at a minimum amoxicillin dose of 60 mg/kg/day

   [2] cefdinir prescribed at a minimum dose of 10 mg/kg/day
3. Parental report of clinical improvement[3]

   [3] based on lack of either subjective or known fever (temperature ≥38.3°C in the preceding 24 hours); current respiratory rate no greater than 50 breaths/minute (<2 years of age) or 40 breaths/minute (≥ 2 years of age); and current grade of cough <3.
4. Ability of a parent or guardian to understand and comply with the study procedures and be available for all study visits
5. Signed written informed consent by a parent or guardian

5.2 Subject Exclusion Criteria

Subjects will be excluded from the study if they meet ANY of the following criteria:

1. Treatment with any systemic antibiotic therapy within 7 days before the diagnosis of CAP

2. Initial therapy for CAP with combination antibiotic therapy[4]

   [4] *amoxicillin, amoxicillin/clavulanate or cefdinir plus one or more additional oral, intravenous, or intramuscular antibiotics*

3. History of anaphylaxis or severe drug allergy to amoxicillin, if prescribed amoxicillin or amoxicillin/clavulanic acid; or oral cephalosporin antibiotics (except cefaclor), if prescribed cefdinir
4. Presence of concomitant bacterial infection that requires >5 days of antibiotic therapy
5. Radiographic findings (where applicable) of complicated pneumonia[5] at presentation or any subsequent chest radiograph up to the time of enrollment

   [5] *Clinically significant pleural effusion, lung abscess, or pneumatocele*

6. Hospitalization[6] for pneumonia during Day -5 to -1 of antibiotic therapy for CAP

   [6]*Subjects who require serial clinical assessments, but are discharged within 24 hours will not be considered hospitalized and will not satisfy this exclusion criterion.*

7. Pneumonia due to *S. aureus* or group A streptococcus documented by positive blood culture or PCR, at the time of enrollment.
8. History of pneumonia within the previous 6 months
9. History of persistent asthma[7] within the previous 6 months or current acute asthma exacerbation[8]

   [7] *Persistent asthma is defined as receiving daily asthma maintenance therapy such as inhaled corticosteroids, cromolyn, theophylline, or leukotriene receptor antagonists.*

   [8] *Acute asthma exacerbation is defined as receiving concomitant bronchodilator therapy and systemic corticosteroids.*

10. Provider-diagnosis of aspiration pneumonia, bronchiolitis, or bronchitis.
11. Surgery or other invasive procedures of the upper or lower airway (e.g., bronchoscopy, laryngoscopy) with general anesthesia or hospitalization ≤7 days before diagnosis of CAP
12. History of an underlying chronic medical condition[9]

[9] *including chronic heart disease, chronic lung disease (except asthma),congenital anomalies of the airways or lung, cystic fibrosis, chronic renal disease including nephrotic syndrome, protein-losing enteropathy of any cause, severe malnutrition, neurocognitive disorders, metabolic disorders (including phenylketonuria), or genetic disorders (note: genetic syndromes such as Down syndrome and Edwards Syndrome are excluded; however, children with genetic disorders (e.g., hemophilia) but who do not have a genetic syndrome may not satisfy this particular exclusion criterion;* it is important that children with such genetic disorders do not have symptoms and/or comorbidities that would pose additional risk to them nor jeopardize the adequacy of study assessments.")

13. History of a condition that compromises the immune system[10]

    [10] *HIV infection, primary immunodeficiency, anatomic or functional asplenia; receipt of a hematopoietic stem cell or solid organ transplant at any time; receipt of immunosuppressive therapy including chemotherapeutic agents, biologic agents, antimetabolites or radiation therapy during the past 12 months; or daily use of systemic corticosteroids for more than 7 consecutive days during the past 14 days.*

14. Any other condition that in the judgment of the investigator precludes participation because it could affect the safety of the subject
15. Current enrollment in another clinical trial of an investigational agent
16. Previous enrollment in this trial

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Per International Conference 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. Subjects will be assigned to either placebo or active study drug (the same antibiotic that they were prescribed for the first 5 days of treatment). After a subject is enrolled, they will be given a random treatment assignment of study product to either short course or standard course therapy. Randomization to short vs. standard course therapy will be at a 1:1 ratio (approximately 200 subjects per treatment group). Subjects will be stratified by age group <24 months vs. 24-71 months), type of initial antimicrobial therapy, and initial treatment in an ED or outpatient clinic/urgent care center.

Enrollment of subjects will be performed online using AdvantageEDC. The list 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 volunteer a treatment code from the list after the necessary data have been entered into the system. A designated individual 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.

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.

5.3.2 Masking Procedures

This is a double-blind clinical trial. The study subjects and their parents/guardians, investigators, and study team staff will remain blinded to study treatment assignment throughout the study. The subjects and their families, investigators, and study team staff will not be blinded to which of

the three antibiotics (amoxicillin, amoxicillin-clavulanate, cefdinir) the subject was initially prescribed.

The study products and placebo will be prepared by the unblinded site Research Pharmacist. Only the preparing pharmacist will be aware of the study product bottle assignments. For subjects randomized to standard course therapy, the pharmacy will provide the same medication prescribed initially. For subjects randomized to short course therapy, the pharmacy will provide a placebo that resembles the appearance (color and texture), flavor, and consistency of the active study product. All study products will be packaged with an identical appearance. Additional details regarding dispensing procedures will be included in the protocol-specific MOP.

The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation. The unblinded site Research Pharmacist will be the only person to perform the unmasking if needed. Additional details regarding labeling procedures will be included in the protocol-specific MOP.

During the consenting process it will be explained to the parents of any potential subjects that the study product (treatment or placebo) that will be provided for administration after Day 5, may or may not taste exactly the same as the originally prescribed medication, and that the look and smell may be slightly different because it might be supplied by a different manufacturer than that of the initially prescribed antibiotic. Parents will also be instructed that the amount or frequency of the prescribed study product has been made uniform across all study groups; therefore, the amount/frequency may be different than originally prescribed by their provider (e.g., receipt of once daily cefdinir is not excluded, but upon study entry, those subjects will receive either twice daily cefdinir or placebo).

5.3.3 Reasons for Withdrawal

Subject Withdrawal
Subjects' parents/guardians 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
- Any new information becomes available that makes further participation unsafe.

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

Discontinuation of Treatment
A subject may be discontinued from treatment and continue to be followed if any of individual halting rules, as defined in Section 9.5.2, are met.

5.3.4 Handling of Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Parents/guardians will be encouraged to complete the Early Termination Visit, as listed in Section 7.5. Unless they expressly state that they wish to have no additional follow-up or data collection, subjects who withdraw from the study will receive a follow-up phone call approximately one week after their withdrawal. This will allow the site to assess the status of the subject and determine if any medical follow up care was sought. Although subjects are free to withdraw at any time or may be withdrawn by the site PI or appropriate sub-investigator at any time, subjects will be encouraged to remain in this study for follow-up assessments (may be by telephone rather than in person) continuing through approximately 1 month after study treatment.

Every attempt will be made to follow all ongoing solicited events or serious adverse events, as well as new-onset chronic medical conditions, to resolution or until the subject's condition becomes stable.

Subjects who discontinue treatment will be followed according to the study protocol and will not be replaced.

5.3.5 Termination of Study

The National Institute of Allergy and Infectious Diseases (NIAID), the IRB of record, or the FDA 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 would 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

Amoxicillin

Amoxicillin, USP is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is similar to penicillin in its bactericidal action against susceptible bacteria during the stage of active multiplication. It acts through the inhibition of cell wall biosynthesis that leads to the death of the bacteria.

Amoxicillin-Clavulanate

Amoxicillin-Clavulanate is an oral antibacterial combination consisting of semisynthetic antibiotic amoxicillin and the beta-lactamase inhibitor, clavulanate potassium. Clavulanic acid is particularly active against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins.

Cefdinir

Cefdinir is an extended-spectrum, semisynthetic cephalosporin. Bactericidal activity of cefdinir results from inhibition of cell wall synthesis and is stable in the presence of some, but not all, beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

6.1.1 Acquisition

Amoxicillin, Amoxicillin-Clavulanate, and Cefdinir will be obtained by the DMID Clinical Materials Services (CMS, Fisher BioServices). The matching placebo for each active drug will be will be prepared by a compounding pharmacy and stored at the DMID CMS.

The compounding, filling, packaging and labeling of study drug placebos will be done according to applicable regulatory requirements. All active study drugs and placebos will be acquired through the DMID CMS.

Study product (amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos) will be shipped from the DMID CMS to the study site upon request and approval by DMID.

6.1.2 Formulation, Packaging, and Labeling

6.1.2.1 Amoxicillin

Amoxicillin will be supplied as an oral powder for suspension in the following strength: 400mg/ 5mL packaged in 100mL bottles. The 400mg/5mL strength contains 400mg of amoxicillin as the trihydrate in each 5mL of reconstituted suspension.

6.1.2.2 Placebo for Amoxicillin

Placebo will be supplied as matching liquid. In order to maintain the blind, the liquid placebo will be formulated for the same appearance (color and texture), flavor and consistency as the active study drug and will be provided in 100mL bottles.

6.1.2.3 Amoxicillin-Clavulanate

Amoxicillin-clavulanate will be supplied as an oral powder for suspension in the following strength: 400mg/ 5mL packaged in 100mL bottles. The 400mg/ 5mL strength contains 400mg of amoxicillin and 57mg of clavulanic acid as a potassium salt in each 5mL of reconstituted suspension. Each 5mL of the 400mg/ 5mL strength contains 0.29mEq of potassium. The 400mg/ 5mL formulations contain aspartame and should not be used by phenylketonurics.

6.1.2.4 Placebo for Amoxicillin-Clavulanate

Placebo will be supplied as matching liquid. In order to maintain the blind, the liquid placebo will be formulated for the same appearance (color and texture), flavor and consistency as the active study drug and will be provided in 100mL bottles.

6.1.2.5 Cefdinir

Cefdinir will be supplied as a white to off-white oral powder for suspension in the following strengths: 125mg/ 5mL and 250mg/ 5mL packaged in 100mL bottles. The 125mg/ 5mL strength contains 125mg of cefdinir in each 5mL of reconstituted suspension. The 250mg/ 5mL strength contains 250mg of cefdinir in each 5mL of reconstituted suspension. Each 5mL of the 250mg/ 5mL strength contains 1.37g of sucrose and each 5mL of the 125mg/5mL strength contains 1.5g of sucrose. Certain formulations from different manufacturers may contain up to 2.86g of sucrose per 5mL.

The lower strength (125mg/ 5mL) will be used in the lower weight bands (or as originally prescribed prior to enrollment) and the higher strength (250mg/ 5mL) will be used in the higher weight bands (or as originally prescribed prior to enrollment) as described in the protocol-specific MOP.

6.1.2.6 Placebo for Cefdinir

Placebo will be supplied as matching liquid for each of the active strengths provided. In order to maintain the blind, the liquid placebo will be formulated for the same appearance (color and texture), flavor and consistency as the active study drug and will be provided in 100mL bottles.

6.1.2.7 Packaging and Labeling

The active study drug will be supplied in their original manufacturer's bottles. The placebo supplied for each active study drug will be filled and packaged by the compounding pharmacy. Each container will also be labeled in compliance with applicable regulatory requirements, including the FDA-required cautionary statement *"Caution- New drug -Limited by Federal (or United States) Law to Investigational Use Only."* As per Section 6.2.2, at the time of study product preparation, the site pharmacist will transfer the contents of the active and placebo into identical containers and affix with blinded labels for dispensing to the subject.

6.1.3 Product Storage and Stability

6.1.3.1 Amoxillin

Store dry powder at 20˚C to 25˚C (68˚F to 77˚F) [See USP Controlled Room Temperature] for unreconstituted powder

Upon reconstitution, when stored under refrigeration or room temperature, any remaining or unused portion must not be used after 14 days. Refrigerated storage is preferred, but not required.

6.1.3.2 Placebo for Amoxicillin

Store the suspension at 2°C to 8°C.

To maintain the blind, upon dispensing, parents/caregivers will be given the same storage instructions as the active drug.

6.1.3.3 Amoxicillin-Clavulanate

Store dry powder at 20˚C to 25˚C (68˚F to 77˚F) [See USP Controlled Room Temperature].

Upon reconstitution, the suspension must be stored under refrigeration and any remaining or unused portion must not be used after 10 days

6.1.3.4 Placebo for Amoxicillin-Clavulanate

Store the suspension at 2°C to 8°C.

To maintain the blind, upon dispensing, parents/caregivers will be given the same storage instructions as the active drug.

6.1.3.5 Cefdinir

Store dry, unsuspended powder at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

Upon reconstitution, the suspension must be stored at room temperature and any remaining or unused portion must not be used after 10 days.

6.1.3.6 Placebo for Cefdinir

Store the suspension at 2°C to 8°C.

To maintain the blind, upon dispensing, parents/caregivers will be given the same storage instructions as the active drug.

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

6.2.1 Dosage

Subjects will complete five days of their originally prescribed antibiotic and then take 5 days of the study product, as follows:

Amoxicillin and Amoxicillin-Clavulanate

Amoxicillin and Amoxicillin-Clavulanate will be dosed based on the amoxicillin component as 80-100 mg/kg/day (maximum 2000 mg/day) divided twice daily.

The matching placebo will be dosed at the same volume calculated for the active dose.

Cefdinir

Cefdinir will be dosed as 12-16 mg/kg/day (maximum 600mg/ day) divided twice daily.

The matching placebo will be dosed at the same volume calculated for the active dose.

6.2.2 Preparation

The site Research Pharmacist must be unblinded and will prepare the active and placebo study products for dispensing to the subject.

Instructions for reconstitution of each active drug will be provided in the protocol-specific MOP. Upon reconstitution, active amoxicillin, amoxicillin-clavulanate, and cefdinir will be transferred from their original commercial containers into new containers strictly for blinding/masking purposes. The matching placebo liquid will be transferred into identical containers to maintain the blind.

Additional details regarding subsequent labeling, preparation of kits, and procedures for dispensing or administration of study product will be described in the protocol-specific MOP.

6.2.3 Administration

All active and placebo study products will be orally administered via oral dosing syringe or dosing cup. For older children in whom a dosing cup is preferred, parents will be instructed to measure the drug in the oral dosing syringe prior to transferring to the dosing cup.

6.3 Modification of Study Intervention/Investigational Product for a Participant

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)

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 will be retained until monitored and released for disposition as per the Sponsor.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

The investigator will maintain records documenting all study products administered to each subject for the entire study period. Subjects will be asked to complete a memory aid and bring their study product containers. The memory aid will be used to record daily study medication taken, concomitant medications (e.g., pain medication), temperature, solicited events, and presence of cough. The study coordinator/investigator will document any missed doses of study medication and provide counseling per study sites' routine procedures to promote compliance with study medication. 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 medication compliance will be obtained by parental interview. The study coordinator/investigator will record how study drug compliance information was obtained. In addition, study product containers will be collected. Study product which has been dispensed and has been returned to the pharmacy should be documented in the study product accountability log and discarded as biohazardous waste.

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 through the last study visit or early termination. 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 chronic medical disease or condition.

Medications that might interfere with the evaluation of the study product or may compromise participant 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 affiliated with the study clinical trial centers. Providers will be informed about the study and provided with site-specific SCOUT-CAP provider information pamphlets summarizing the study design and participant eligibility criteria. Providers may also be asked to alert their patients about their practice's participation in the SCOUT-CAP 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 new pneumonia cases from medical records.

Once a potentially eligible subject with the diagnosis of CAP is identified, study staff will first contact the treating clinic to confirm willingness to have the patient participate in the study. For subjects deemed potentially eligible, study staff will attempt to contact the parent(s)/guardian(s) by telephone. If the parent(s)/guardian(s) are contacted successfully, the study staff may use the telephone contact guide (see MOP). Study staff will explain the study protocol and describe the inclusion/exclusion criteria. Study staff will answer any questions and concerns the parent(s)/guardian(s) may have. If the parent(s)/guardian(s) are interested in the study, study staff will schedule the Enrollment Visit on Day -3 to Day -1 of antibiotic therapy.

Parents/caregivers of potential subjects who express interest in participation will be contacted again by study staff prior to the Enrollment Visit to confirm the appointment time and location and to assess the presence of ongoing symptoms such as fever, respiratory rate, and cough. If fever, elevated respiratory rate, or Grade 3 cough are present, the visit may be rescheduled for a later day, but no later than before receipt of the first dose of their initially prescribed antibiotic on the sixth consecutive calendar day of treatment. In all instances, the parent/guardian will be instructed to continue administration of original antibiotic as instructed by the treating clinician until the Enrollment Visit.

7.2 Enrollment/Baseline

At the Enrollment Visit, study staff will obtain written informed consent from the parent(s)/guardian(s) for the primary study and request consent for collection of throat swabs and stool specimens for future use. Declination to participate in collection of future use samples will not affect participation in the primary study. After the parent/guardian has had the opportunity to ask questions and has signed the informed consent document, the following activities will be performed by the study staff:

- Eligibility criteria will be reviewed;
- A complete medical history and sociodemographic data will be obtained by interview with the subject's parent(s)/legal guardian;

- A physical assessment will be performed to determine general appearance, hydration status; vital signs, including temperature, heart rate, and respiratory rate; an assessment of work of breathing; and presence of skin rash; additionally, if indicated by the physical assessment or medical history, a physical examination by a study clinician may occur;

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

- An initial assessment of clinical response will be obtained to include report of subjective fever, maximum temperature in the past 24 hours (if taken), and an assessment of improved activity and appetite since initiating antibiotic therapy;

- All concomitant medications taken within 30 days of signing the informed consent form will be recorded;

- Subjects who meet eligibility criteria will be enrolled in AdvantageEDC^{SM} and randomly assigned to one of two arms: standard course therapy (5 days of active medication) vs. short course therapy (5 days of matching placebo);

- Study product will be dispensed and study staff will review the study product with the subject's family and review the study product storage and dosing instructions;

- Subjects will be provided with a memory aid and other study-related materials to record daily temperature, solicited events, concomitant medications, presence of cough, and daily dose administration. Parents will be instructed that any temperatures over 100.9˚F should be repeated 15 minutes later in the same manner as the initial temperature. Study staff will instruct the parent/guardian to complete the memory aid in order to document adherence and to bring the medication bottle with them to the Outcome Assessment Visit #1. Study staff will also review the memory aid used to assess specific, solicited events;

- Collection of a throat swab specimen if contributing future use samples;

- Dispense containers for collection of a stool specimen, if participating in future use portion of the study.

Since the Enrollment Visit will occur during Day 3-5 of treatment (Day -3 to -1), the subject will be instructed to complete the originally prescribed medication through Day -1 (after receipt of the last dose of the originally prescribed medication on the fifth consecutive calendar day of treatment) and to start study product on Day 1.

Parents will be educated at the time of their child's enrollment in the study about prompt and adequate treatment for recurrence of symptoms or solicited events. The subject's parent/guardian will be instructed to contact their primary care provider as soon as possible in the event of worsening respiratory status, recurrence of fever, or for other concerns. Parents/guardians will also be asked to contact study personnel in the event of clinical deterioration (i.e., medical visit or hospitalization for pneumonia) or for any severe solicited events.

Study personnel will be available at each site for urgent issues related to the study or for communication with primary care providers who may have questions about the study.

Subjects who do not meet eligibility criteria or decline consent will be instructed to continue their initially prescribed antibiotic unless otherwise advised by their treating clinician.

7.3 Follow-up

Visit 2: Outcome Assessment Visit #1, Day 6-10

Subjects will be seen for a follow-up visit on Day 6-10. Prior to this visit, study staff will, when possible, 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;
- The subject received non-study, systemic antibiotic therapy;
- The subject underwent drainage of pleural fluid, placement of a chest tube, or video assisted thoracoscopic surgery.

At the follow-up visit, study staff will complete the following procedures:

- Medical history to determine whether medically attended visits, receipt of non-study systemic antibiotics, or surgical procedures have occurred;
- Assessment of adequate clinical improvement as indicated by a parental report of lack of rectal, tympanic, axillary or oral temperature ≥38.3°C or 100.9°F, normalization of respiratory rate for age (<50 breaths/minute for children <24 months of age and <40 breaths/minute for children 24-71 months of age), and grading of cough.
- Physical assessment to determine vital signs (temperature, pulse and respiratory rates) and physical assessment (general appearance, hydration status, work of breathing, presence of skin rash);
- Review of the subject's memory aid to assess and record any solicited events and concomitant medications;
- Review of potential protocol-defined SAEs;
- Review of memory aid to assess treatment compliance;
- Collection of study product bottle for drug accountability, if available;
- Collection of a throat swab and stool specimen (if available), if consented for future use samples.

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 child 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 primary physician.

7.4 Final Study Visit

Visit 3: Outcome Assessment Visit #2, Day 19-25

Subjects will be seen for a follow-up visit on Day 19-25. 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 since the previous visit.

- The subject had a medically attended visit to an ED, urgent care, or clinic;
- The subject was hospitalized;
- The subject received non-study, systemic antibiotic therapy;
- The subject underwent drainage of pleural fluid, placement of a chest tube, or video assisted thoracoscopic surgery.

At the follow-up visit, study staff will complete the following procedures:

- Medical history to determine whether medically attended visits, receipt of non-study systemic antibiotics, or surgical procedures have occurred;
- Assessment of adequate clinical improvement as indicated by a parental report of lack of rectal, tympanic, axillary, or oral temperature ≥38.3°C or 100.9°F for >24 hours, normalization of respiratory rate for age (<50 breaths/minute for children <24 months of age and <40 breaths/minute for children 24-71 months of age), and grading of cough.
- Physical assessment to determine vital signs (temperature, pulse, and respiratory rate) and physical assessment (general appearance, hydration status, work of breathing, presence of skin rash);
- Review of the subject's memory aid to assess and record any solicited events and concomitant medications;
- Review of potential protocol-defined SAEs
- Review of memory aid assess treatment compliance (if not reviewed at Visit 2);
- Collection of study product bottle for drug accountability, if not collected at Visit 2 and if available
- Collection of a throat swab and stool specimen (if available), if consented for future use samples.

If the subject develops signs or symptoms of pneumonia (including fever, increased work of breathing, or increased cough) or develops a severe solicited event, the child 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 primary physician.

7.5 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 outcome assessment visits except no throat swab or stool specimen (if consented to participate in the collection of future use samples) will be collected. Unless they expressly state that they wish to have no additional

follow-up or data collection, subjects who withdraw from the study will receive a follow-up phone call approximately one week after their withdrawal. Study staff will review the memory aid and determine if any follow-up medical care was sought.

If the subject presents with symptoms such as fever and/or elevated respiratory rate at the Early Termination visit, the study team will inform the subject's PCP/pediatrician and will urge the parent(s) to follow-up with their primary provider.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

A screening medical history will be obtained by interview of subject's parents/caregivers during the prescreening telephone call and will be confirmed at the time of enrollment. Parent(s)/ guardian(s) will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, or other chronic medical conditions will be obtained. 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.

Medication history (concomitant medications) will include a review of all current medications and medications taken within 30 days prior to signing the informed consent form through the last study visit. All 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 the enrollment visit, a physical assessment to assess eligibility will occur, which will include vital signs (temperature, pulse and respiratory rates); hydration status; an assessment of work of breathing; and presence of skin rash. If indicated based on subject's medical history or physical assessment, a more complete physical examination (conducted by a study clinician licensed to make medical diagnoses and listed as an investigator on the Form FDA 1572) may occur. An initial assessment of clinical response will be obtained to include maximum temperature in the past 24 hours and an assessment of improved activity and appetite since initiating antibiotic therapy.

An assessment of clinical response will occur at each follow-up visit. The assessment will include parental documentation of maximum temperature in the preceding 24 hours; normalization of respiratory rate; presence and extent of cough; occurrence of medically attended visits including visits to the ED, primary care physician, and urgent care; hospitalizations; use of non-study systemic antibiotics (parenteral or oral); and occurrence of surgical procedures. Vital signs (temperature, pulse and respiratory rates) will be collected at the enrollment visit and at each follow-up visit.

Solicited event assessments will include an assessment of solicited events occurring from the time of enrollment through the last visit, Visit 3. All subjects will complete a subject memory aid from the time of enrollment through Visit 3. Subject memory aids will be reviewed with the subject's parents for any discrepancies or missing data and will be returned to the subject's parent(s).

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

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

8.2.2 Special Assays or Procedures

N/A

8.2.3 Specimen Preparation, Handling, and Shipping

N/A

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

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

If the subject's parent/legal guardian consents to future use, clinical site personnel will obtain throat swabs and arrange collection of stool samples. Routine throat swabs will be obtained by site personnel at the time of enrollment, Outcome Assessment Visit #1, and Outcome Assessment Visit #2. Please refer to the MOP for specific details regarding type of swab. At enrollment, parents will be provided with a stool collection kit and instructions for sample collection. Parents will collect a stool sample within 2 days after the enrollment visit and within 2 days prior to or 2 days after Outcome Assessment Visits #1 and #2. Parents will be instructed to immediately store the stool sample in their home freezer. Parents will be instructed to bring the stool samples to the clinical site or sites will arrange pickup (e.g., courier services) at the subject's home. Samples will be transported to the laboratory in a freezer pack; once at the laboratory, samples will be stored at approximately -20°C, with temporary excursions up to -5˚C allowable. The microbial community composition has been shown to remain consistent in fecal samples stored at room temperature for up to 24 hours and for up to 14 days at 4°C or -20°C.[9,10] Moreover, samples are stable for up to 6 months at -80°C.[9,10]

Throat Swabs

Samples will be stored locally in an approximately 4˚C refrigerator, with temporary excursions up to 8˚C allowable, for up to 48 hours after collection. Samples will then be held in a -20˚C freezer (with temporary excursions to -5˚C allowable) until they are batch shipped to the DMID Clinical Materials Services (CMS).

Stool Samples

Stool specimens will be obtained at Visits 1, 2, and 3. Specimens will be collected by retention of a fecal containing diaper or by collection of stool into a sterile cup that will be provided to the subject's parent/legal guardian. Samples can be collected within 2 days of the study visit and maintained in a freezer in the subject's home until sent by courier or collected by study staff and transported to the study site. A minimum of approximately 2 teaspoons of stool will be collected. Samples will be stored locally and shipped according to Section 8.2.3.2.

8.2.3.2 Specimen Shipment

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

All specimens will be transported or shipped via courier under controlled conditions to the site (if collected at a home visit or affiliated clinic) and stored according to the MOP in order to maintain appropriate storage temperatures. When requested, samples will be batch-shipped to the DMID CMSper instructions in the MOP.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Amoxicillin, amoxicillin-clavulanate, cefdinir are approved drugs with established and well-described safety profile. The most prevalent of the drug side effects include:

Amoxicillin: Common side effects include rash, diarrhea, nausea, vomiting, and mucocutaneous candidiasis. Rare side effects include:

- Cardiovascular: hypersensitivity angiitis
- Central nervous system: agitation, anxiety, behavioral changes, confusion, dizziness, headache, hyperactivity (reversible), insomnia, seizure
- Dermatologic: acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Gastrointestinal: dental discoloration (brown, yellow, or gray; rare), hemorrhagic colitis, melanoglossia, pseudomembranous colitis
- Genitourinary: crystalluria
- Hematologic & oncologic: agranulocytosis, anemia, eosinophilia, hemolytic anemia, leukopenia, thrombocytopenia, thrombocytopenic purpura
- Hepatic: cholestatic hepatitis, cholestatic jaundice, hepatitis (acute cytolytic), increased hepative enzymes
- Hypersensitivity: anaphylaxis
- Immunologic: serum sickness-like reaction

Amoxicillin-clavulanate (in addition to side effects listed for amoxicillin above): Common side effects include diaper rash, abdominal discomfort, and loose stools. Other reported side effects include:

- Dermatologic: diaper rash, urticaria
- Gastrointestinal: abdominal distress, diarrhea, loose stools, nausea, vomiting
- Genitourinary: vaginitis
- Infection: candidiasis, vaginal mycosis
- Rare but important or life-threatening: cholestatic jaundice, headache, hepatotoxicity (idiosyncratic), increased liver enzymes, increased serum alkaline phosphatase, prolonged prothrombin time, thrombocythemia, vasculitis (hypersensitivity)

Cefdinir: Common side effects include rash, abdominal pain, nausea, vomiting, diarrhea, headache, and mucocutaneous candidiasis. Other side effects include:

- Central nervous system: headache
- Endocrine & metabolic: decreased serum bicarbonate, glycosuria, hyperglycemia, hyperphosphatemia, increased gamma-glutamyl transferase, increased lactate dehydrogenase
- Genitourinary: Proteinuria, occult blood in urine, urine alkalinization
- Hematologic: eosinophilia, lymphocytopenia, lymphocytosis, thrombocythemia, anemia
- Hepatic: increased serum alkaline phosphatase, increased serum ALT

- Rare but important or life-threatening: anaphylaxis, anorexia, blood coagulation disorder, bloody diarrhea, cholestasis, conjunctivitis, erythema multiforme, erythema nodosum, fulminant hepatitis, hemolytic anemia, hepatitis (acute), interstitial pneumonitis (idiopathic), pseudomembranous colitis, renal failure (acute), and Stevens-Johnson syndrome

As amoxicillin, amoxicillin-clavulanate, cefdinir are approved drugs with long prescribing history, NIAID does not expect that any new drug related safety signal will be detected in this trial. As such, the safety data collection will be targeted to only collect protocol defined SAEs and Suspected Unexpected Serious Adverse Reaction (SUSAR, See Section 9.2.2).

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

9.2.1 Adverse Events

Adverse Event (AE): International Conference 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.

As the safety profile of amoxicillin, amoxicillin-clavulanate, and cefdinir are well established, and this trial is not powered to detect new, unknown safety signals, **there will be no unsolicited AE collection during this study and only protocol-defined SAE's will be collected**.

Solicited adverse events that are common and known to occur following administration of the study product. Solicited adverse events will be recorded daily for the duration of the study (See Table 3) . In addition to the solicited adverse events specified in Table 3, the presence and severity of cough (Table 2) will be recorded daily for the duration of the study to allow for assessment of the resolution of pneumonia symptoms.

9.2.2 Serious Adverse Events

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event[1],
- inpatient hospitalization or prolongation of existing hospitalization,

[1] Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, might have caused death.

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Protocol defined SAEs: For this protocol, only the following SAEs will be collected, regardless of the relationship to study drug.

- Death that is not the result of trauma or accident
- Anaphylaxis
- Laryngospasm or bronchospasm within 1 day after initiation of the study treatment
- Stevens-Johnson syndrome
- Severe erythema multiforme
- Toxic epidermal necrolysis

SAEs must be graded for severity and assessed for relationship to study product (see definitions below).

Severity of Event: SAEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.

- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.

- Severe (Grade 3): Events interrupt the subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Relationship to Study Product: The study physician's assessment of an SAE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in this study. If there is any doubt as to whether a clinical observation is an SAE, the event should be reported. The relationship to study product must be assessed for SAEs using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.3 Procedures to be Followed in the Event of Abnormal Clinical Findings

Subjects will be evaluated for the adequacy of clinical response and for the occurrence of solicited events at the outcome assessment visits. If a serious adverse event is suspected, or if clinical response is inadequate, subjects will be referred immediately to their primary provider or local ED/urgent care.

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

All SAEs will be:

- Assessed for severity and causal relationship by a physician listed on the Form FDA 1572 as the principal investigator (PI) or sub-investigator.
- Recorded on the appropriate SAE report form.
- Followed through resolution by a study physician.
- Reviewed by the safety monitor, the DSMB (periodic review unless associated), DMID Medical Monitor, and the local IRB.

Death, life-threatening events, hospitalization or prolongation of existing hospitalization, and other important medical events are part of the efficacy endpoints of this trial and will not be reported or collected as SAEs, unless meeting the SAE reporting criteria included in Section 9.2.2.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20814, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, selected SAE data fields must also be entered into the Emmes AdvantageEDC web-based data entry system. Refer to the Manual of Procedures for details regarding this procedure. Timelines for submission of an SAE form are as follows:

- All non-accidental deaths and life-threatening events, regardless of relationship, will be recorded on the SAE form and sent by fax within 24 hours of site awareness of the death or event.
- All other SAEs, regardless of relationship, will be reported via fax by the site within 24 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the subject to be stable.

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site principal investigator or appropriate sub-investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating site principal investigators (i.e., all principal investigators to whom the sponsor is providing drug under its IND(s) or under any principal investigator's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Study related solicited events will be followed until the final study visit.

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, 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 2 subjects (or >2% if more than 100 subjects enrolled) that requires intensive care or leads to death due to persistent/worsening pneumonia

- More than five subjects (>5% if more than 100 subjects enrolled) experience persistent/worsening pneumonia within 3 days of initiation of study treatment
    - Persistent/worsening pneumonia is a clinical diagnosis, accompanied by the following clinical characteristics:
        - administration of non-study directed systemic antibiotic therapy, hospitalization, or surgical intervention (e.g., placement of a chest tube) for persistent/worsening pneumonia
- More than 2 subjects (>2% if more than 100 subjects enrolled) experience an SAE of laryngospasm, bronchospasm, or anaphylaxis within 1 day after initiation of study treatment that is suspected to be related to study product.
- More than 2 subjects (>2% if more than 100 subjects enrolled) experience death (that is not the result of trauma or accident) within 3 days of initiation of study treatment and is suspected to be related to study product.

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
- 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.

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 participant, 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 participant, clinical, and safety data that may include enrollment and demographic information, medical history, concomitant medications, physical assessments, dosing, solicited events, and SAEs. 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. The DMID Medical Monitor will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during the study.

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 any issues noted

In this protocol, a ‘specific site’ is defined as one in which resources for the study (e.g., study staff, storage facilities, drug storage, or study records) are housed. Monitoring visits will focus on these specific sites to ensure compliance with DMID and ICH/GCP policies, procedures, and guidelines. In addition, a significant number of visits will occur in non-site locations, such as community clinics or home visits. These ‘generic’ sites will not be considered part of the site monitoring plan.

11 STATISTICAL CONSIDERATIONS

This is a randomized double-blinded placebo-controlled trial comparing a strategy of short course (5-days) vs. standard course (10-days) oral beta-lactam antibiotic therapy with respect to desirability of outcome in children with CAP.

The trial is designed using Response Adjusted for Days of Antibiotic Risk (RADAR).[11] RADAR utilizes a superiority trial design under the conceptual framework, evaluating whether a strategy of short course antibiotic therapy is better than the standard course strategy when considering the totality of all of the important outcomes (adequacy of the clinical response, adverse events, and the duration of antibiotic use).

All trial participants are assigned a desirability of outcome ranking (DOOR), constructed as follows:

I. Each subject is evaluated according to the ordinal clinical response (Refer to Section 3.2.1)

II. DOOR is assigned according to two rules:

(i) When comparing two subjects with different ordinal clinical responses, the subject with a better ordinal clinical response receives a higher rank.

(ii) When comparing two subjects with the same ordinal clinical response, the subject with fewer days of antibiotic use receives a higher rank. Days of antibiotic use are defined as the number of days for which the subject is reported to have taken at least one dose of non-placebo study product or a non-study product systemic antibiotic.

During analyses, the distributions of DOORs are compared between short-course and standard-course strategies. The sum of the probability that a randomly selected participant from the short course strategy will have a better DOOR than a randomly selected participant from the standard course strategy plus one-half the probability that the DOORs are equal is estimated using a confidence interval.

The primary outcome measure is the DOOR at Outcome Assessment Visit #1 (defined above). DOOR at Outcome Assessment Visit #1 is computed using data from Day 1 to Day 5.

Secondary outcome measures include:

1. DOOR at Outcome Assessment Visit #2.
2. Resolution of symptoms (a component of DOOR) at each outcome assessment visit, defined as the absence of fever, tachypnea, or cough of grade 2 or higher.
3. Adequate clinical response rates (a component of DOOR) at each outcome assessment visit, defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
4. Frequency of solicited events at each outcome assessment visit, as listed in Table 3.

5. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for persistent or worsening pneumonia (as defined above) at each outcome assessment visit
   i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.
6. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for all causes at each outcome assessment visit
   i. Individual event types (e.g., medical visits, hospitalizations surgical procedures, and receipt of non-study systemic antibiotic) will be compared between treatment groups.

Exploratory outcome measures include:

1. DOOR at Outcome Assessment Visits #1 and #2, when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a one day difference to a two, three, four, or five day difference.

11.1 Study Hypothesis

- Null: the sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

11.2 Sample Size Considerations

The primary study sample size is based on a superiority test of the null hypothesis in 11.1, under an assumed alternative hypothesis that the sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 60% (p=60%).

A sample size of 360 (180 per arm) provides 90% power using a 2-sided alpha=0.05 with a Wilcoxon Mann-Whitney U test. If p=65% or 70%, then a total sample size of 160 (80 per arm) or 90 (45 per arm), respectively, would be required. The sample size is inflated by ~10% based on an estimate from a similar study, in order to account for loss to follow-up resulting in a total sample size of 400 (200/arm).

11.3 Planned Interim Analyses

11.3.1 Safety Review

A Data Safety Monitoring Board (DSMB) appointed by NIAID will monitor this protocol. Interim safety review may include enrollment and demographic information, medical history, concomitant medications, physical assessments, dosing, and protocol specific SAEs and SUSAR. 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 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 the study or to modify or terminate the study.

Additionally, the study will be monitored to determine if any of the halting rules described in Section 9.5 are met.

11.3.1 Interim Analysis of Efficacy, Futility, and Safety

One interim analysis, described below, will be performed and reported to the DSMB after at least 30% of the targeted subjects have completed the study. The interim analysis will inform DSMB decisions regarding stopping early for efficacy, futility, or safety.

For the interim analysis, a snapshot of the study database will be unblinded and used to conduct analyses as follows. An ITT analysis including all enrolled subjects in the snapshot of the study database will be performed, testing the null hypothesis provided in Section 11.1 using the methods described in Section 11.4.1, with the modification that the Haybittle-Peto boundary ($p<0.001$) will be used when concluding statistical significance. The study may be stopped early for efficacy only if statistical significance is detected in that test. In the event of statistical significance, sensitivity analyses using complete case and according-to-protocol cohorts (CC-V1 and ATP-V1, as described below) as well as worst case analyses will be included in the DSMB report to further guide decisions for stopping for efficacy.

A 95% confidence interval for the probability that a randomly selected subject will have a better DOOR if assigned to the 5-day strategy (vs. the standard strategy) will be estimated but not used to inform DSMB decisions about stopping early for efficacy. Predicted interval plots (PIPS)[12,13] will be constructed to provide the DSMB with a prediction of the trial results were the trial to continue as planned under varying assumptions regarding future data (e.g., current trend continues, null hypothesis is true, alternative hypothesis is true).

The DSMB will also be provided with the following:

1. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a between arm difference in the overall outcome (DOOR) via a cumulative difference plot with respective confidence bands for Outcome Assessment Visit #1

2. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics at Outcome Assessment Visit #1.

3. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) Oral, rectal, axillary or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding Outcome Assessment Visit #1, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia; (2) Elevated respiratory rate (RR >50

breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at Outcome Assessment Visit #1, and (3) Presence of cough Grade 2 or 3 at Outcome Assessment Visit #1.

4. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of each solicited event and with the risk difference of any solicited event, for each severity threshold (mild or greater, moderate or greater, or severe) for Outcome Assessment Visit #1.

11.4 Final Analysis Plan

The primary analysis of the primary endpoint will be performed according to an intention-to-treat (ITT) approach and include all randomized subjects. As (secondary) sensitivity analyses of the primary endpoint, complete case analyses using the CC-V1 / ATP-V1 cohorts (defined below) and a worst case analysis using the ITT cohort of the primary endpoint will be performed. Additional analyses may be performed and are described in detail in the Statistical Analysis Plan.

Intention-to-Treat Cohort: All randomized participants, analyzed as randomized. Subjects that have not received at least one dose of study product will have adequate clinical response and its sub-components treated as missing.

Complete Case Cohorts (CC): Subjects in a CC analysis are analyzed as randomized, but excluded from analysis if missing data prevents assigning an unambiguous value to the DOOR endpoint or if the subject has not received at least one dose of study product. The CC-V1 cohort will consist of all subjects with sufficient data to define unambiguously the Visit #1 DOOR. The CC-V2 cohort will consist of all subjects with sufficient data to define unambiguously the Visit #2 DOOR.

According-to-Protocol Cohorts (ATP): Subjects in an ATP analysis require at least one dose of study product each day from Day 1 to Day 5 and furthermore subjects will excluded from analysis if missing data prevents assigning an unambiguous value to the DOOR endpoint The ATP-V1 cohort will restrict subjects to those with sufficient data to define unambiguously the Visit #1 DOOR. The ATP-V2 cohort will restrict subjects to those with sufficient data to define unambiguously the Visit #2 DOOR.

Details of what constitutes sufficient data to assign an unambiguous value to DOOR will be specified in the statistical analysis plan.

11.4.1 Primary Analysis

For the primary analyses, the DOORs will be compared between the 5- and 10-day arms. The sum of the probability that a randomly selected subject will have a better DOOR if assigned to the 5-day arm for Outcome Assessment Visit #1 plus one-half the probability of equal DOORs for Outcome Assessment Visit #1 will be estimated. The null hypothesis to be tested is that the probability is equal to 0.50 (lack of superiority of short-course therapy). The primary analysis will be carried out using the ITT cohort, with missing DOOR values (treated as continuous)

imputed using multiple imputation, utilizing linear regression models corresponding to relevant observed data (baseline covariates and observed DOOR components from an early termination visit, if available). The Mann-Whitney U statistic will be combined across the datasets to give the test statistic and Rubin's Rules used to define distribution of the test statistic under the null hypothesis. The test of the null hypothesis will be two-sided with a Type I error of 0.05. A point estimate of the estimand will be computed by dividing combined test statistic by the number of pairwise comparisons and a confidence interval of the estimand will be computed by inverting the described test of the null hypothesis.

Note: Subjects will be asked to confirm fever with repeat testing after approximately 15 minutes; for analysis purposes, subjects lacking a repeat measurement will be considered as having developed fever.

11.4.2 Secondary Analyses

All secondary and exploratory analyses will use a Type I error rate of 0.05 and will not correct for multiple comparisons. All tests will be two-sided.

Secondary analyses will include:

- Analysis of DOOR at Outcome Assessment Visit #2, performed as ITT in an analogous manner to the primary analysis.

- Sensitivity Analyses for the DOOR at Outcome Assessment Visits #1 and #2 ITT analyses. (1) CC analyses. (2) ATP analyses. (3) Worst case analyses: all imputations of missing data will be the worst case (result in the lowest possible DOOR given available information) for subjects in the 5-day arm and best case for subjects in the 10-day arm. Sensitivity analyses will test the null hypothesis using the Mann-Whitney U Test, estimate using U divided by the number of pairwise comparisons, and will compute confidence intervals by (1) inverting the Mann-Whitney U Test and (2) using a non-parametric bootstrap.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of each solicited event and the risk difference of <u>any</u> solicited, for each severity threshold (mild or greater, moderate or greater, or severe). Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) Oral, rectal, axillary or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding the Outcome Assessment Visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia; (2) Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit; and (3) Presence of cough Grade 2 or 3 at the Outcome Assessment Visit. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for all causes: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics. Tests for differences in proportions between treatment arms will be given by Fisher's exact tests.

- Analysis of the ordinal clinical response at Outcome Assessment Visits #1 and #2. The ITT analysis will treat the ordinal clinical response as Normal distributed and use multiple imputation to compute confidence intervals for the mean ordinal clinical response by treatment assignment and to test whether the mean ordinal clinical response varies by treatment assignment. CC, ATP, and worst case analyses of the ordinal clinical response will be performed; separately for Outcome Assessment Visit #1 and #2, a cumulative difference plot with respective 95% confidence bands for the ordinal clinical response (and an associated result from a Mantel-Hantzel chi-square test on the ordinal clinical response) will be computed. Non-inferiority analyses of the ordinal clinical response at Outcome Assessment Visits #1 and #2 using the ITT cohort, to be specified in the statistical analysis plan, may be carried out.

11.4.3 Exploratory Analyses

Increased RADAR thresholds sensitivity analysis. In the primary RADAR/DOOR analysis, if two subjects from separate treatment arms have an equal ordinal clinical response but a difference in the duration of antibiotic use of at least $k = 1$ day, RADAR assigns a more favorable response to the subject with fewer days of antibiotic use. For a sensitivity analysis, the effect of increasing the minimum difference in the duration of antibiotic use ($k = 2,3,4,$ or 5) before a favorable response is given to the subject with shorter duration of antibiotic use will be explored. For each value of k, bootstrapped confidence intervals of the probability of more favorable DOOR due to assignment to the 5-day antibiotic course will be computed and plotted versus k. Analysis will be performed separately for DOOR at Outcome Assessment Visit #1 and DOOR at Outcome Assessment Visit #2. Analyses will be performed using CC-V1/CC-V2 cohorts.

Other exploratory analyses, if required, to be specified in the statistical analysis plan.

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 ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate 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. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or 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 trial. Data collection forms will be derived from the eCRFs and be provided by the Statistical and Data Coordinating Center (SDCC).

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating VTEU sites and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The 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. The 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 beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

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.

14.3 Informed Consent Process

14.3.1 Informed Consent

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.

Local IRB requirements will govern subject recruitment efforts and pre-enrollment 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.

14.3.2 Informed Consent/Assent Process (in Case of a Minor)

Parents or legal guardians will be asked to provide consent for the participation of their children as outlined in Section 14.3.1. Since all eligible children in this study are <7 years of age, formal written assent will not be obtained; nevertheless, study personnel will explain the study to the child in age appropriate terms and will ensure that the well being of participating children is protected.

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

This study is focused on children age 6-71 months of age and will include 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. If a written contract for the conduct of the trial which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

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 Future Use of Stored Specimens

Subjects will be asked for permission to keep any samples for use in future research studies, such as analyzing the impact of antibiotic usage of the microbiome. Some samples may be stored at the local site and some at a central clinical storage facility. Samples may be shared with other investigators at other institutions, provided that appropriate human subject protection plans are in place. The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on samples. 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 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, 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 statistical reports may be generated as deemed necessary and appropriate by DMID. Safety and efficacy summary reports may be generated for the DSMB.

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 for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified. 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

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

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APPENDIX A – SCHEDULE OF EVALUATIONS

	Initial treatment of CAP and Eligibility Screening[1]	Enrollment Visit	Receipt of Study Agent[2]	Outcome Assessment Visit #1	Outcome Assessment Visit #2	Early Termination Visit (as applicable)
Visit Number		1		2	3	
Visit Day	Days -5 to 1	Day -3 to -1	Days 1-5	Day 6-10	Day 19-25	
Screening and Enrollment						
Initially prescribed antibiotic therapy	X					
Review of electronic medical records to assess eligibility[3]	X					
Phone contact with parent/guardian to assess eligibility	X					
Obtain Informed Consent		X				
Review Eligibility Criteria		X				
Medical History[4]		X		X	X	X
Concomitant Medications		X		X	X	X
Vital Signs (temperature, pulse, respiratory rate)		X		X	X	X
Physical Assessment[5]		X		X	X	X
Assess clinical response to initial antibiotic therapy		X				
Enrollment and Randomization		X				
Dispense study agent[2]		X				
Distribute Memory Aid and Study-Related Materials		X				
Follow-up						
Receipt of study agent			X			
Collection of study product bottle				X	X[7]	X[7]
Review of electronic medical record to assess clinical response[6]				X	X	X
Review Memory Aid				X	X	X
Assess clinical response to therapy				X	X	X
Assess solicited events				X	X	X
Collection of Future Use Samples (if consented)						
Throat Swab		X		X	X	
Collection of stool		X		X	X	

Footnotes:

1. Day -5 is defined as the date on which the diagnosis of CAP is made and treatment with oral beta-lactam therapy is initiated.
2. Study drug will be either a continued course of the oral antibiotic therapy that was initially prescribed (oral amoxicillin, amoxicillin-clavulanate, or cefdinir) or a 5 day course of matching placebo, which will begin on Day 1.
3. Electronic medical records will be used to preliminarily assess eligibility, including: age of the subject; diagnosis of CAP (a diagnosis of "pneumonia" is sufficient) without additional diagnoses of bronchiolitis or croup; initial antibiotic therapy for CAP with sufficient dose (i.e., prescription of amoxicillin or amoxicillin/clavulanate with an amoxicillin dose of 80-100 mg/kg/day or prescription of cefdinir of 12-16 mg/kg/day); absence prescription of any other antibiotic therapy ≤7 days before the diagnosis of CAP; absence of initial antibiotic therapy for CAP with combination therapy (i.e., amoxicillin, amoxicillin/clavulanate or cefdinir plus one or more additional antibiotics),; absence of a history of allergy to amoxicillin or oral cephalosporin antibiotics (except cefaclor); absence of radiographic findings of complicated pneumonia (pleural effusion, lung abscess, or pneumatocele) on the initial chest radiograph (if obtained) or any subsequent chest radiograph; absence of hospitalization for pneumonia during day 1-5 of antibiotic therapy for CAP; absence of blood or pleural fluid culture positive for *S. aureus* or group a streptococcus; absence of history of other conditions as described on the exclusion criteria; any other condition that in the judgment of the investigator precludes participation because it could affect the safety of the subject; current participation in any other clinical trial.
4. Medical history will include acute or chronic medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency and autoimmune disease will be solicited. The history will include capture of sociodemographic data.
5. A physical assessment will be performed to determine general appearance and hydration status; vital signs, including temperature, pulse, and respiratory rate; an assessment of work of breathing, and presence of skin rash. This can be performed by a nurse, advanced practice nurse, physician assistant, pr physician.
6. Study staff will make a preliminary EHR-based assessment of clinical response to determine whether any of the following events occurred after initiation of study drug: a medically attended visit to an ED or outpatient clinic; receipt of non-study antibiotic [parenteral or oral]; treatment for a local pneumonia complication, including drainage of pleural fluid, placement of a chest tube, or video assisted thoracoscopic surgery.
7. If not collected at previous visit.

CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 14-0079
Study Title:
A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)

NCT02891915

Version 1.0

DATE: 11-MAY-2018

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 14-0079**
Development Phase:	Phase IV
Products:	Amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos
Form/Route:	Oral suspensions
Indication Studied:	Community Acquired Pneumonia
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	04OCT2016
Clinical Trial Completion Date:	DDMMMYYYY
Date of the Analysis Plan:	26APR2018
Version Number:	0.4 (DRAFT)

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

ACR	Adequate Clinical Response
AE	Adverse Event/Adverse Experience
ATC	Anatomical Therapeutic Classification
ATP	According-to-Protocol
CAP	Community Acquired Pneumonia
C	Celsius
CAR	Clinical Agents Repository
CC	Complete Case
CC-V1	Complete Case at Outcome Assessment Visit #1 Analysis Population
CC-V1	Complete Case at Outcome Assessment Visit #2 Analysis Population
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOOR	Desirability of Outcome Ranking
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EHR	Electronic Health Record
F	Fahrenheit
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
h	Hours
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDES	Internet Data Entry System

LIST OF ABBREVIATIONS *(continued)*

IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-to-Treat
kg	Kilogram
L	Liter
MAR	Missing at Random
MAV	Medically Attended Visit
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
N	Number (typically refers to subjects)
NIH	National Institutes of Health, DHHS
OAV	Outcome Assessment Visit
OCR	Ordinal Clinical Response
OHRP	Office for Human Research Protections
PI	Principal Investigator
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
RADAR	Response Adjusted for Days of Antibiotic Risk
RR	Respiratory Rate
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SCOUT	Short Course Therapy for Urinary Tract Infections in Children

LIST OF ABBREVIATIONS *(continued)*

SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
Std	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
USP	United States Pharmacopeia

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)" (DMID protocol 14-0079) describes and expands upon the statistical information presented in the protocol.

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

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

2. INTRODUCTION

This is a Phase IV, blinded, placebo-controlled, multi-center, randomized trial with a primary objective to compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with community acquired pneumonia (CAP) assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy. Subjects are randomized 1:1 to either an additional 5 day course of their initially prescribed antibiotic (10 days total antibiotic therapy), or 5 days of a matching placebo (5 days total antibiotic therapy). Randomization is stratified by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility). Randomization is not stratified by clinical site.

The study follows a variety of clinical outcomes including 1) persistence of fever, tachypnea, or cough; 2) medically attended visits for persistent or worsening pneumonia; and 3) solicited events.

2.1. Purpose of the Analyses

A composite of the clinical outcomes and number of days of antibiotic use is used to define the DOOR and assess the overall superiority of short course treatment. Superiority of DOOR using clinical outcomes from the first 5 study days and at Outcome Assessment Visit #1 will be the primary analysis. Superiority of DOOR using clinical outcomes from the first 18 days and at Outcome Assessment Visit #2 will be a secondary analysis. For both analyses, all components of the DOOR will also be analyzed individually.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

1. To compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days).

3.1.2. Secondary Objectives

1. To compare the composite overall outcome (DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #2 (Study Day 22 +/- 3 days).
2. To compare the resolution of symptoms (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.
4. To compare solicited events (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.
5. To compare medically attended visits to Emergency Departments (ED) or outpatient clinics, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics (components of the clinical response) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.

3.1.3. Exploratory Objectives

1. To examine the robustness of results of DOOR comparisons when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a 1 day difference to a 2, 3, 4, or 5 day difference.

3.2. Endpoints

3.2.1. Primary Endpoints

The primary endpoint/outcome measure is the DOOR at Outcome Assessment Visit #1.

3.2.2. Secondary Endpoints

Secondary outcome measures include:

1. DOOR at Outcome Assessment Visit #2
2. Resolution of symptoms (a component of DOOR) at each outcome assessment visit, defined as the absence of fever, tachypnea, or cough of grade 2 or higher.
3. Adequate clinical response rates (a component of DOOR) at each outcome assessment visit, defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
4. Frequency of solicited events at each outcome assessment visit, as listed in Table 3.
5. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for persistent or worsening pneumonia (as defined below) at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.
6. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for all causes at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations surgical procedures, and receipt of non-study systemic antibiotic) will be compared between treatment groups.

3.2.3. Exploratory Endpoints

1. DOOR at Outcome Assessment Visits #1 and #2, when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a 1 day difference to a 2, 3, 4, or 5 day difference.

3.3. Study Definitions and Derived Variables

DOOR is defined as follows:

1. Each subject is evaluated according to the ordinal composite outcome (See Table 1) and assigned an outcome rank ranging from 1-8. The ordinal outcome is referred to elsewhere in the SAP as the ordinal clinical response (OCR).
2. Desirability of Outcome Ranking (DOOR) is then assigned according to two rules:
    i. When comparing two subjects with different ordinal responses, the subject with a better ordinal response receives a higher rank.
    ii. When comparing two subjects with identical ordinal responses, the subject with fewer days of antibiotic use receives a higher rank.

The ordinal composite outcome involves an assessment of whether the subject has an adequate clinical response and whether they have experienced any solicited events as defined in Table 1.

Table 1: Ordinal Outcome

	Adequate clinical response[1] (Assessed at Outcome Assessment Visits #1 and #2)	Solicited events[3] (Assessed at Outcome Assessment Visits #1 and #2)
1	Yes, with resolution of symptoms[2]	None
2	Yes, with resolution of symptoms[2]	Mild (Grade 1)
3	Yes, with resolution of symptoms[2]	Moderate (Grade 2)
4	Yes, with resolution of symptoms[2]	Severe (Grade 3)
5	Yes, with persistent symptoms of fever, tachypnea, or cough	None or any grade
6	No, with ED/clinic visit but no hospitalization	None or any grade
7	No, with hospitalization	None or any grade
8	Death from any cause	

[1] Adequate clinical response is defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
• Persistent or worsening pneumonia is defined as receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
• Note: Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.
[2] Resolution of symptoms is defined as the absence of all of the following:
• Oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding the Outcome Assessment Visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia;
• Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit;
• Presence of cough grade 2 or 3 at the Outcome Assessment Visit, defined as Grade 0 (no cough), Grade 1 (Occasional coughing [less than 4 times hourly]), Grade 2 (frequent coughing [4 or more times an hour], interferes with sleep), Grade 3 (almost constant coughing (never free of cough), makes sleep nearly impossible);
[3] Solicited events will be captured daily until Outcome Assessment Visit #2; thereafter, parents/legal guardians will report symptoms based on memory aid and medical interview by study staff. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Day 1: Day 1 begins at the time the first dose of study product is administered and ends at 11:59 PM of that same day. If a subject has no recorded receipt of study product at the time of the analysis, then Day 1 will be defined as the date 5 days after the date of initiation of the initial antibiotic.

DOOR at Outcome Assessment Visit #1: Defined as above, using DOOR components from the following Study Days.

Adequate Clinical Response: Day 1 – Day 5

Resolution of Symptoms:

- Fever as measured in the 24 hours prior to Outcome Assessment Visit #1. If a subject has a fever according to a single measurement, but no repeat measurement after at least 15 minutes has been performed, the subject will be analyzed as having a fever. If a subject has a fever according to the measurement taken as a part of vital signs

during Outcome Assessment Visit #1, the subject will be analyzed as having a fever at Outcome Assessment Visit #1. If the vital signs measurement shows no fever, and the parental assessment of fever during the previous 24 hours is missing, then fever will be treated as missing.

- Respiratory Rate and Cough: determined at Outcome Assessment Visit #1

Solicited Events: Day 1 – Day 5

Number of Days of Antibiotic Use: Day 1 – Day 5

DOOR at Outcome Assessment Visit #2: Defined as above, using DOOR components from the following Study Days.

Adequate Clinical Response: Day 1 – Day 18

Resolution of Symptoms:

- Fever as measured in the 24 hours prior to Outcome Assessment Visit #2. If a subject has a fever according to a single measurement, but no repeat measurement after at least 15 minutes has been performed, the subject will be analyzed as having a fever. If a subject has a fever according to the measurement taken as a part of vital signs during Outcome Assessment Visit #2, the subject will be analyzed as having a fever at Outcome Assessment Visit #2. If the vital signs measurement shows no fever, and the parental assessment of fever during the previous 24 hours is missing, then fever will be treated as missing.
- Respiratory Rate and Cough: determined at Outcome Assessment Visit #2

Solicited Events: Day 1 – Day 18

Number of Days of Antibiotic Use: Day 1 – Day 18

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a multi-center, randomized, double-blind, placebo-controlled, superiority clinical trial evaluating short course (5 day) vs. standard course (10 day) of oral beta-lactam antibiotic therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) for treatment of CAP in children 6-71 months of age who have clinically improved prior to enrollment. The study will randomize approximately 400 enrolled subjects to one of the two study arms (approximately 200 children in each arm) in order to reach 360 evaluable subjects. Subjects will be randomized (1:1) to receive either a standard course of the initially prescribed antibiotic (10 days) or a short course of the initially prescribed antibiotic (5 days) plus 5 days of matching placebo.

The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Day -5 is defined as the date on which oral beta-lactam therapy is initiated for a diagnosis of CAP. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. These subjects will be assessed for eligibility and enrolled on Day -3 to -1 of their initially prescribed oral beta-lactam therapy. Subjects may also be enrolled on Day 1 (the first day of receipt of study agent) provided they have not yet received any doses of the healthcare provider-prescribed antibiotic therapy for that day.

Visit 1: Enrollment Visit. Subjects who meet the eligibility criteria, and whose parent/guardian consents for participation in the study, will complete an Enrollment Visit on Day -3 to -1. Subjects satisfying the inclusion criteria with no exclusion criteria will be enrolled and randomized. Enrolled subjects will continue to receive the initially prescribed antibiotic through Day -1. The subjects' parents/guardians will be instructed to contact study personnel if their child develops fever or worsening respiratory symptoms (worsening cough, increased work of breathing, any other concerning symptoms in the parents' estimation) following enrollment.

Randomization: Enrolled subjects will be randomized to short vs. standard course therapy at a 1:1 ratio, with stratification by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility).

Intervention: Subjects will continue on the initially prescribed antibiotic through Day -1, until they have completed 5 days (i.e., 5 scheduled doses of once daily medication, 10 scheduled doses of twice daily medication) of antibiotic therapy [e.g., if a subject takes the first dose of antibiotic in the afternoon of Day -5, the first dose of study agent would occur on the afternoon of Day 1, providing 10 total scheduled doses of a twice daily prescribed antimicrobial]. The first day of receipt of study agent will be Day 1. Subjects assigned to standard course therapy will receive 5 additional days (10 doses) of the same initially prescribed antibiotic, with standardized twice-daily dosing. Subjects assigned to short course therapy will receive 5 more days (10 doses) of a matching placebo. Both the study agent and placebo may appear different than the commercial formulation the child originally received. The placebo will appear indistinguishable in color, taste, thickness, and consistency from the active antibiotic the child would otherwise

receive in the study. The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation.

Follow-up and Assessment of Endpoints: Subjects will be scheduled for the following assessment visits:

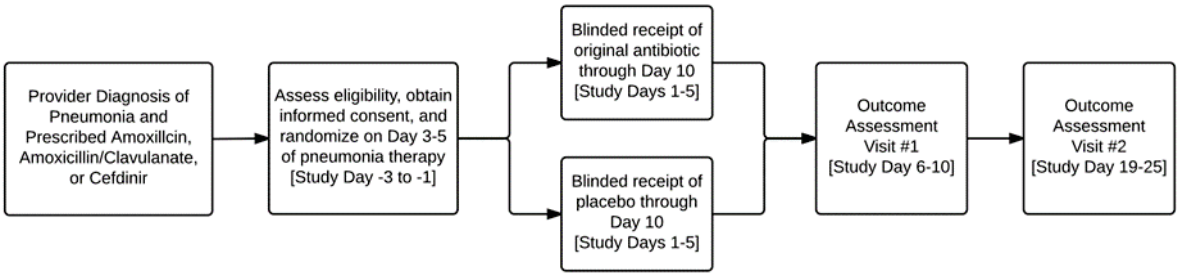
Visit 2: Outcome Assessment Visit #1, Day 6 to 10 (1-5 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Visit 3: Outcome Assessment Visit #2, Day 19 to 25 (14-20 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects who are identified as having an inadequate clinical response prior to Outcome Assessment Visit #1 will be asked to complete Outcome Assessment Visits #1 and #2, in order to evaluate the occurrence of any solicited events and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects will be invited to contribute oropharyngeal and stool specimens at specified times throughout the study for future use. Additional informed consent will be obtained for future use sample collection.

Figure 1: Schematic of the Study Design



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

In 2014, a randomized trial of short vs. standard course therapy in young children in Israel with CAP suspected to be of bacterial origin found a higher rate of treatment failure (40%) in subjects treated for only 3 days vs. subjects treated for 5 or 10 days (Greenberg 2014). The study was underpowered to detect a difference in treatment failure between subjects treated for 5 vs. 10 days, but treatment failure did not occur in either group.

The proposed study will test the effectiveness of short (5-day) vs. standard (10-day) course therapy in children who are diagnosed with CAP and initially treated in outpatient clinics, urgent

care facilities, and emergency departments. The study will specifically address whether short course therapy is superior to standard therapy among children that have clinically improved since diagnosis. If superior to standard course therapy, short course therapy could reduce antibiotic exposure among young children. We will use a study methodology similar to the SCOUT Study ("Short Course Therapy for Urinary Tract Infections in Children")—a randomized, double-blind, placebo-controlled non-inferiority trial of short course antimicrobial therapy for urinary tract infection in children sponsored by NIAID through the "Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance" initiative. However, the SCOUT-CAP trial will use a superiority study design using an ordinal composite overall outcome (Desirability of Outcome Ranking, DOOR, see Protocol Section 3.2.1 Primary Outcome Measures)—to test the hypothesis that short course (5 day) therapy is superior to standard course (10-day) beta-lactam therapy in children who have experienced early clinical improvement of pneumonia.

The potential risk of short course therapy is that clinical outcomes may not be equivalent to standard course therapy. Specifically, the percent of children with adequate clinical response (or in this case, no relapse of illness) may be lower in children receiving short course therapy. Adequate clinical response can be defined as resolution or substantial improvement in clinical signs and symptoms (e.g., fever, cough, respiratory rate, work of breathing) and the lack of need for additional antibiotic therapy, additional contacts with the health care system, or surgical procedures for worsening pneumonia. The magnitude of this risk is not well established, although a study from Israel suggests it is small (Greenberg 2014); nevertheless, this degree of risk will be evaluated during this trial.

4.3. Selection of Study Population

Subjects who are diagnosed with CAP in emergency departments (EDs), urgent care facilities, and clinics will be screened for eligibility. Screening will continue until 400 subjects are enrolled cumulatively across all the study sites. The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on antibiotic therapy using oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. Other forms and/or mechanisms of recruitment may also be used. The local IRB will approve recruitment materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

4.3.1. Inclusion Criteria

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

4.3.2. Exclusion Criteria

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

4.3.3. Reasons for Withdrawal

Subject Withdrawal

Subjects' parents/guardians 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
- Any new information becomes available that makes further participation unsafe.

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

Discontinuation of Treatment

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

4.4. Treatments

4.4.1. Treatments Administered

All active and placebo study products will be orally administered via oral dosing syringe or dosing cup. For older children in whom a dosing cup is preferred, parents will be instructed to measure the drug in the oral dosing syringe prior to transferring to the dosing cup.

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

Per International Conference 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. Subjects will be assigned to either placebo or active study drug (the same antibiotic that they were prescribed for the first 5 days of treatment). After a subject is enrolled, they will be given a random treatment assignment of study product to either short course or standard course therapy. Randomization to short vs. standard course therapy will be at a 1:1 ratio (approximately 200 subjects per treatment group). Subjects will be stratified by age group <24 months vs. 24-71 months), type of initial antimicrobial therapy, and initial treatment in an ED or outpatient clinic/urgent care center.

Enrollment of subjects will be performed online using the electronic data capture (EDC) system provided by the Statistical and Data Coordinating Center (SDCC). The list of randomized treatment assignments will be prepared by statisticians at the SDCC. The list will be used to assign each volunteer a treatment code after the necessary data have been entered into the EDC

system. A designated individual 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.

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

4.4.3. Blinding

This is a double-blind clinical trial. The study subjects and their parents/guardians, investigators, and study team staff will remain blinded to study treatment assignment throughout the study. The subjects and their families, investigators, and study team staff will not be blinded to which of the three antibiotics (amoxicillin, amoxicillin-clavulanate, cefdinir) the subject was initially prescribed.

The study products and placebo will be prepared by the unblinded site Research Pharmacist. Only the pharmacy staff will be aware of the study product bottle assignments. For subjects randomized to standard course therapy, the pharmacy will provide the same medication prescribed initially. For subjects randomized to short course therapy, the pharmacy will provide a placebo that resembles the appearance (color and texture), flavor, and consistency of the active study product. All study products will be packaged with an identical appearance. Additional details regarding dispensing procedures will be included in the protocol-specific MOP.

The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation. The unblinded site Research Pharmacist will be the only person to perform the unmasking if needed. Additional details regarding labeling procedures will be included in the protocol-specific MOP.

During the consenting process it will be explained to the parents of any potential subjects that the study product (treatment or placebo) that will be provided for administration after Day 5, may or may not taste exactly the same as the originally prescribed medication, and that the look and smell may be slightly different because it might be supplied by a different manufacturer than that of the initially prescribed antibiotic. Parents will also be instructed that the amount or frequency of the prescribed study product has been made uniform across all study groups; therefore, the amount/frequency may be different than originally prescribed by their provider (e.g., receipt of once daily cefdinir is not excluded, but upon study entry, those subjects will receive either twice daily cefdinir or placebo).

4.5. Study Variables

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

As the safety profile of amoxicillin, amoxicillin-clavulanate, and cefdinir are well established, and this trial is not powered to detect new, unknown safety signals, there will be no unsolicited event collection during this study and only protocol-defined SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected.

For a complete list of SAEs that will be collected, regardless of the relationship to the study drug, see the Protocol. SAEs will be graded for severity and assessed for relationship to study product.

See the Protocol for the schedule of events for this study.

Severity of Event: SAEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Relationship to Study Product: The study physician's assessment of an SAE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in this study. If there is any doubt as to whether a clinical observation is an SAE, the event should be reported. The relationship to study product must be assessed for SAEs using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

All SAEs will be:

- Assessed for severity and causal relationship by a physician listed on the Form FDA 1572 as the principal investigator (PI) or sub-investigator.
- Recorded on the appropriate SAE report form.
- Followed through resolution by a study physician.
- Reviewed by the safety monitor, the DSMB (periodic review unless associated), DMID Medical Monitor, and the local IRB.

Death, life-threatening events, hospitalization or prolongation of existing hospitalization, and other important medical events are part of the efficacy endpoints of this trial and will not be reported or collected as SAEs, unless meeting the SAE reporting criteria included in the Protocol.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group.

In addition to the SAE form, selected SAE data fields must also be entered into the EDC web-based data entry system. Refer to the Manual of Procedures for details regarding this procedure. Timelines for submission of an SAE form are as follows:

- All non-accidental deaths and life-threatening events, regardless of relationship, will be recorded on the SAE form and sent by fax within 24 hours of site awareness of the death or event.
- All other SAEs, regardless of relationship, will be reported via fax by the site within 24 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the subject to be stable.

5. SAMPLE SIZE CONSIDERATIONS

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

H0: The sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

The primary study sample size is based on a superiority test of the null hypothesis above, under an assumed alternative hypothesis that the sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 60% (p=60%).

A sample size of 360 (180 per arm) provides 90% power using a 2-sided alpha=0.05 with a Wilcoxon Mann-Whitney U test (see calculation below). If p=65% or 70%, then a total sample size of 160 (80 per arm) or 90 (45 per arm), respectively, would be required. The sample size is inflated by ~10% based on an estimate from a similar study, in order to account for loss to follow-up resulting in a total sample size of 400 (200/arm).

Sample size calculations were based on the formula below (Noether 1987):

$$N = \frac{\left(z_\alpha + z_\beta\right)^2}{12c(1-c)\left(p'' - \frac{1}{2}\right)^2}$$

$z_\alpha = \Phi^{-1}(0.975);\ z_\beta = \Phi^{-1}(0.90)$; (90% power for two-sided test with 5% Type I error)

$c = 0.5$ (equal allocation to treatment arms)

$p'' = 0.6$ (Pr(Higher DOOR) under alternative hypothesis)

Note that the primary analysis statistical methods use the ITT analysis population and will account for missing data with multiple imputation. The exact analysis method was not used for the power calculation because it would require an excessive amount of assumptions about the nature and patterns of missing data in the final dataset and relationships of components of the imputation model to the primary outcome. Instead, a complete case analysis assuming 90% evaluable for analysis was used to obtain approximately 90% power in the actual analysis.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

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

6.2. Timing of Analyses

One interim analysis will be performed and reported to the data and safety monitoring board (DSMB) after approximately 30% of the targeted subjects have completed the study. The interim analysis will inform DSMB decisions regarding stopping early for efficacy, futility, or safety.

The final analysis will be performed after database lock.

6.3. Analysis Populations

The primary analysis will be performed using the intention-to-treat (ITT) cohort. Other analyses, as specified below, may use complete case (CC) or according-to-protocol (ATP) cohorts. Analyses of the ITT cohort will include imputation for missing data, while analyses of CC and ATP cohorts will not contain missing data by design, because they are required to have sufficient data to define unambiguously the Outcome Assessment Visit #1 DOOR or Outcome Assessment Visit #2 DOOR.

Reasons for exclusion from each analysis population are summarized in Table 5 and shown by subject in Listing 4. Excluded subjects might satisfy multiple criteria justifying their exclusion, but will have only one reason indicated in Table 5 and Listing 4. The reason indicated will be determined by the following rules.

CC-V1 Exclusions

- Subject not treated with study product
- Not excluded for any reason above, but early termination before Outcome Assessment Visit #1 (subjects will be tabulated by reason for termination)
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Adequate Clinical Response
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Resolution of Symptoms
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Solicited Event Severity Days 1-5
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Number of Days of Antibiotic Use

CC-V2 Exclusions

- Subject not treated with study product
- Not excluded for any reason above, but early termination before Outcome Assessment Visit #2 (subjects will be tabulated by reason for termination)
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Adequate Clinical Response
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Resolution of Symptoms
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Solicited Event Severity Days 1-18
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Number of Days of Antibiotic Use

ATP-V1 Exclusion Reasons

- The subject was excluded from CC-V1 cohort
- Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5
- Not excluded for any reason above, major protocol deviation (see Section 6.3.3; subjects will be tabulated by type of protocol deviation)

ATP-V2 Exclusion Reasons

- The subject was excluded from CC-V2 cohort
- Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5
- Not excluded for any reason above, major protocol deviation (see Section 6.3.3, subjects will be tabulated by type of protocol deviation)

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

The ITT cohort will include all randomized subjects. The analyses on the ITT cohort will be performed per randomized treatment assignment.

Subjects randomized but not treated will be analyzed in the ITT cohort, but will have adequate clinical response and its components treated as missing. Therefore, in ITT analyses, OCR and DOOR will be missing and will need to be imputed for subjects that were not treated. If data (solicited events, cough, etc.) are collected post-randomization for a subject that was not treated, that data will be used in the ITT analysis to assist in imputing the OCR and DOOR.

6.3.2. Complete Case (CC) Cohorts

Subjects in a CC analysis are analyzed as randomized, but excluded from analysis if missing data prevents assigning an unambiguous value to the DOOR endpoint or if the subject has not received at least one dose of study product. The CC-V1 cohort will consist of all subjects with sufficient data to define unambiguously the Outcome Assessment Visit #1 DOOR. The CC-V2

cohort will consist of all subjects with sufficient data to define unambiguously the Outcome Assessment Visit #2 DOOR.

6.3.3. According-to-Protocol (ATP) Cohorts

Subjects in an ATP analysis require no major protocol deviations, and recorded receipt of at least one dose of study product each day from Day 1 to Day 5. What constitutes a major protocol deviation will be assessed on a case-by-case basis by a DMID/VTEU/ARLG committee prior to any member of the committee being unblinded to treatment assignments. Subjects in an ATP analysis will be analyzed as treated. The ATP-V1 cohort will restrict subjects to those in CC-V1 that furthermore meet the ATP requirements. The ATP-V2 cohort will restrict subjects to those in CC-V2 that furthermore meet the ATP requirements.

6.3.4. Safety Analysis Population

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

6.4. Covariates and Subgroups

Subjects will be recruited from multiple clinical sites, but randomization will not be stratified by site. Randomization will use a total of 12 strata, with stratification by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility).

6.5. Missing Data

While all efforts will be made to minimize missing data, some missing data is expected. Whenever possible, subjects terminating from the study early will be given an early termination visit during which the available components of the DOOR and related measures can be recorded. The primary analysis will use multiple imputation with linear models to impute values using available information (treatment, randomization strata variables, and available visit information), assuming a missing at random (MAR) model. Secondary analyses will further examine the robustness of this analysis, including a “worst case analysis” in which all imputations of missing data will be the worst case (result in the lowest possible DOOR given available information) for subjects in the 5-day arm and best case for subjects in the 10-day arm. Day 1 in this study is defined as the date of first receipt of study product. If a subject has no record of study product administration or did not receive a first dose of study product, but has other post-randomization data, Day 1 will be imputed as the date 5 days after the date of first receipt of initial antibiotic.

In some cases, a subject may have DOOR defined despite missing some of its components, in which case the subject will be eligible for inclusion into the CC and ATP analysis populations. In analyses of the components of the DOOR using the CC and ATP analysis populations, data will be analyzed as available and missing data will not be imputed.

The study includes several composite variables with rules for assignment, missingness, and imputation described below.

6.5.1. Adequate Clinical Response to OAV#1 or OAV#2

Subjects that have no record of receipt of at least one dose of study product will have adequate clinical response and its components considered missing at both OAV#1 and OAV#2. Otherwise, if a subject dies at any point during subject participation in the study, the subject will be considered as not having adequate clinical response at OAV#1 or OAV#2. Otherwise, if a subject does not have OAV#1 then ACR and its components are missing for OAV#1 and if a subject does not have OAV#2 then ACR and its components are missing for OAV#2.

Several variables are used to define the Adequate Clinical Response:

- MAVABRX: Was the subject prescribed or did the subject receive an additional antibiotic treatment at this visit? (Yes/No)
    - MAVABCP: If Yes, was the antibiotic given for pneumonia or treatment for a complication of pneumonia? (Yes/No)
- MAVPLEUR: Drainage of pleural fluid as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVCHTB: Placement of a chest tube as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVVIDEO: Video assisted thoracoscopic surgery as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVTHOR: Thoracotomy procedure as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVSURG: Any other surgical procedure as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVHOSP: Was the subject hospitalized at this visit? (Yes/No)
    - MAVHPPN: If Yes, was the hospitalization for the treatment of pneumonia or pneumonia complications? (Yes/No)

If a subject has OAV#1 and did not have a medically attended visit (MAV) from Day 1 to Day 5, inclusive, then the subject had adequate clinical response for OAV#1. If the subject had a MAV from Day 1 to Day 5 for which MAVABRX and MAVABCP were both YES (receipt of a non-study systemic antibiotic for pneumonia), or for which MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were YES (treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures), then the subject did not have adequate clinical response at OAV#1. If the subject had a MAV from Day 1 to Day 5 for which MAVHOSP and MAVHPPN were both YES (subject was hospitalized for the treatment of pneumonia or pneumonia complications), then the subject did not have adequate clinical response at OAV#1. Otherwise, if the subject had a MAV from Day 1 to Day 5 and either MAVABRX was missing, MAVABRX was YES and MAVABCP was missing, or any of MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were missing, then adequate clinical response at OAV#1 is missing. Otherwise, if a subject has one or more MAVs from Day 1 to Day 5, with no MAV indicating receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid,

placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures and no hospitalization for treatment of pneumonia or pneumonia complications and no MAV missing data as described, then the subject has adequate clinical response at OAV#1. Note that for determining whether the medical treatment or hospitalization falls within the period of Day 1 to Day 5, the date of the initial MAV will be used (MAVVISDT), rather than specific dates of surgery or hospitalization entered on the MAV form.

If a subject has OAV#2 and did not have a medically attended visit (MAV) from Day 1 to Day 18, inclusive, then the subject had adequate clinical response for OAV#2. If the subject had a MAV from Day 1 to Day 18 for which MAVABRX and MAVABCP were both YES (receipt of a non-study systemic antibiotic for pneumonia), or for which MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were YES (treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures), then the subject did not have adequate clinical response at OAV#2. If the subject had a MAV from Day 1 to Day 18 for which MAVHOSP and MAVHPPN were both YES (subject was hospitalized for the treatment of pneumonia or pneumonia complications), then the subject did not have adequate clinical response at OAV#2. Otherwise, if the subject had a MAV from Day 1 to Day 18 and either MAVABRX was missing, MAVABRX was YES and MAVABCP was missing, or any of MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were missing, then adequate clinical response at OAV#2 is missing. Otherwise, if a subject has one or more MAVs from Day 1 to Day 18, with no MAV indicating receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures and no hospitalization for treatment of pneumonia or pneumonia complications and no MAV missing data as described, then the subject has adequate clinical response at OAV#2. Note that for determining whether the medical treatment or hospitalization falls within the period of Day 1 to Day 18, the date of the initial MAV will be used (MAVVISDT), rather than specific dates of surgery or hospitalization entered on the MAV form.

The below pseudocode summarizes the logic for defining ACR at OAV#1.

```
if no recorded receipt of study product then ACR_OAV1=missing
else if death then ACR_OAV1=NO
else if subject does not have OAV#1 then ACR_OAV1=missing
else if subject has no MAV from Day 1 to Day 5 then ACR_OAV1=YES
else if subject has one or more MAVs from Day 1 to Day 5 with
      (MAVABRX=YES and MAVABCP=YES) or
      MAVPLEUR=YES or
      MAVCHTB=YES or
      MAVVIDEO=YES or
      MAVTHOR=YES or
      MAVSURG=YES or
      (MAVHOSP=YES and MAVHPPN=YES)
      then ACR_OAV1=NO
else if subject has MAV from Day 1 to Day 5 with
      MAVABRX=missing or
      (MAVABRX=YES and MAVABCP=missing) or
```

```
      MAVPLEUR= missing or
      MAVCHTB= missing or
      MAVVIDEO= missing or
      MAVTHOR= missing or
      MAVSURG= missing

then ACR_OAV1=missing
else ACR_OAV1=YES
```

6.5.2. Fever at OAV#1 or OAV#2

Two variables are used to define Fever at OAV#1 or OAV#2:

- ACRTEMP: Has the subject had a recorded temperature > 38.3 °C (100.9 °F) in the past 24 hours? (Yes/No)
- ACRFEV: If Yes, was fever attributed to a process unrelated to the prior diagnosis of pneumonia? (Yes/No)

Fever at Outcome Assessment Visit #1 and Fever at Outcome Assessment Visit #2 both involve several data components and have complex rules for when they are considered missing versus when fever is considered present or not present. The below logic describes the rules. Note that "fever is observed as a solicited event" only if a temperature of ≥ 38.3 °C (100.9 °F) was recorded on the day of the Outcome Assessment Visit or on the day prior to the Outcome Assessment Visit and either had no recorded confirmatory measurement at least 15 minutes after the first measurement or else the confirmatory measurement also indicated a temperature of ≥ 38.3 °C (100.9 °F). Fever at the OAV is never missing if the OAV did occur (specifically, ACRTEMP not missing), and the vital signs measurement at the visit and the actual temperatures reported by parents and recorded on the solicited events form (SRS) are treated as optional and supplemental data in the determination of the presence of fever at the visit.

- If the OAV did occur
  - If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is not indicated as unrelated to prior diagnoses of pneumonia (ACRFEV), then fever at the OAV is present
  - If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is indicated as unrelated to prior diagnoses of pneumonia (ACRFEV), then fever at the OAV is absent
  - If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is indicated as relatedness to prior diagnoses of pneumonia (ACRFEV) is missing, then fever at the OAV is missing
  - If subject had a recorded temperature < 38.3 °C (100.9 °F) (ACRTEMP), then fever at the OAV is absent

6.5.3. Resolution of Symptoms at OAV#1 or OAV#2

Resolution of symptoms is defined as the absence of all of the following:

- Fever at the OAV, as defined above

- Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit (VS1.RESPB);
- Presence of cough grade 2 or 3 at the Outcome Assessment Visit (ACRCGHSV)

If the subject died at any point of participation in the study then the subject will be analyzed as not having resolution of symptoms at either Outcome Assessment Visit. Otherwise, if the subject did not have adequate clinical response at OAV#1 or OAV#2, then the subject will be analyzed as not having resolution of symptoms at the respective Outcome Assessment Visit(s). Otherwise, if fever, elevated respiratory rate, or presence of grade 2 or 3 cough is indicated at OAV#1 or OAV#2, then the subject does not have resolution of symptoms at the respective Outcome Assessment Visit (regardless of whether some components of the resolution of symptoms are missing). Otherwise, if fever, respiratory rate, and presence of cough are all non-missing at OAV#1 or OAV#2, then the subject has resolution of symptoms at the respective Outcome Assessment Visit. Otherwise, resolution of symptoms is missing at the Outcome Assessment Visit.

6.5.4. Most Severe Solicited Event at OAV#1 and OAV#2

If a subject had severity grades (0 to 3) recorded for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 5, inclusive, then the most severe solicited event at OAV#1 will be the maximum severity grade taken across all solicited events from Day 1 to Day 5. If a subject had any solicited event of severity grade 3 from Day 1 to Day 5, then the most severe solicited event at OAV#1 will be grade 3, regardless of the presence of missing data during that period. Otherwise, if a subject has missing data for the severity grade of any solicited event from Day 1 to Day 5 then most severe solicited event at OAV#1 will be missing.

If a subject had severity grades (0 to 3) recorded for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 18, inclusive, then the most severe solicited event at OAV#2 will be the maximum severity grade taken across all solicited events from Day 1 to Day 18. If a subject had any solicited event of severity grade 3 from Day 1 to Day 18, then the most severe solicited event at OAV#2 will be grade 3, regardless of the presence of missing data during that period. Otherwise, if a subject has missing data for the severity grade of any solicited event from Day 1 to Day 18 then most severe solicited event at OAV#2 will be missing.

6.5.5. Ordinal Clinical Response at OAV#1 or OAV#2

If the subject died at any point of study participation then OCR at OAV#1 will be 8.

Else if the subject has missing ACR at OAV#1 then OCR at OAV#1 will be missing.

Else if the subject did not have ACR at OAV#1 and was hospitalized from Day 1 to Day 5 then OCR at OAV#1 will be 7.

Else if the subject did not have ACR at OAV#1 and was not hospitalized from Day 1 to Day 5 then OCR at OAV#1 will be 6.

Else if the subject has missing resolution of symptoms at OAV#1 then OCR at OAV#1 will be missing.

Else if the subject did not have resolution of symptoms at OAV#1 then OCR at OAV#1 will be 5.

Else if the subject has missing most severe solicited event at OAV#1 then OCR at OAV#1 will be missing.

Else if the subject had a most severe solicited event of grade 3 at OAV#1 then OCR at OAV#1 will be 4.

Else if the subject had a most severe solicited event of grade 2 at OAV#1 then OCR at OAV#1 will be 3.

Else if the subject had a most severe solicited event of grade 1 at OAV#1 then OCR at OAV#1 will be 2.

Else OCR at OAV#1 will be 1.

If the subject died at any point of study participation, then OCR at OAV#2 will be 8.

Else if the subject has missing ACR at OAV#2 then OCR at OAV#2 will be missing.

Else if the subject did not have ACR at OAV#2 and was hospitalized from Day 1 to Day 18 then OCR at OAV#2 will be 7.

Else if the subject did not have ACR at OAV#2 and was not hospitalized from Day 1 to Day 18 then OCR at OAV#2 will be 6.

Else if the subject has missing resolution of symptoms at OAV#2 then OCR at OAV#2 will be missing.

Else if the subject did not have resolution of symptoms at OAV#2 then OCR at OAV#2 will be 5.

Else if the subject has missing most severe solicited event at OAV#2 then OCR at OAV#2 will be missing.

Else if the subject had a most severe solicited event of grade 3 at OAV#2 then OCR at OAV#2 will be 4.

Else if the subject had a most severe solicited event of grade 2 at OAV#2 then OCR at OAV#2 will be 3.

Else if the subject had a most severe solicited event of grade 1 at OAV#2 then OCR at OAV#2 will be 2.

Else OCR at OAV#2 will be 1.

Note that in some cases OCR can be defined even if some components are missing. For instance, if a subject had record of receipt of study product and did not have adequate clinical response at OAV#1, OCR at OAV#1 would still be defined even if most severe solicited event at OAV#1 was missing.

6.5.6. Number of Days of Antibiotic Use at OAV#1 or OAV#2

It will be assumed that all subjects have precisely five days of antibiotic use with the initial antibiotic prior to Day 1 (the day of the first dose of study product). Analysis involving comparisons of the number of days of antibiotic use will consider antibiotic use from Day 1 onwards. The number of days of antibiotic use is defined as the actual number of days of antibiotic use (any amount of study product that is not placebo, or any amount of other systemic antibiotic) from Day 1 to Day 5, inclusive, for OAV#1 and from Day 1 to Day 18 for OAV#2. For subjects that received placebo as study product, it is counted as the number of days of systemic antibiotic as determined solely from the concomitant medication form. For subjects that receive actual antibiotic as study product, it is counted as the number of days that the subject received any amount of either study product or a non-study systemic antibiotic, as determined from the concomitant medication form. Note that missed doses of study product do not necessarily lower the number of days of antibiotic use as long as a separate dose of antibiotic (study product antibiotic or concomitant medication antibiotic) was received on that day. Extra doses of study product beyond the protocol specification of 10 doses count as normal toward the number of days of antibiotic use. The number of days of antibiotic use is missing (at both OAV#1 and OAV#2) if the product administration record was not completed / on record for the subject and the subject did not have antibiotic use during the study period recorded as a concomitant medication. If a subject does not have an OAV#1 or OAV#2, then number of days of antibiotic use at OAV#1 is missing. If a subject does not have an OAV#2, then number of days of antibiotic use at OAV#2 is missing. As exceptions, subjects that were hospitalized due to pneumonia or a complication of pneumonia or the died during the study period will have number of days of antibiotic use at OAV#1 or OAV#2 as 5 if randomized to the standard course or as 0 if randomized to short course if the number of days of antibiotic use at OAV#1 or OAV#2 is missing as defined above.

The number of days of antibiotic use at the time of analysis will be determined from the product administration records and concomitant medication records only. Data management activities and site queries (outside the scope of this document) prior to data lock will ensure concomitant medication records are as complete as possible and consistent with other records (i.e., AEs and medically attended visit records in the clinical database). The number of days of antibiotic use for a concomitant medication will be calculated as the medication end date minus the medication start date plus one day. Days will not be double counted if multiple systemic antibiotics (including antibiotic as study product) are taken on the same day. Systemic antibiotic use will not be counted for days that fall outside of the range being considered (Days 1 to Day 5, or Day 1 to Day 18).

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

number of days of treatment rounded up to the nearest integer for all systemic antibiotics in the concomitant medication records (minus 1).

6.5.7. Desirability of Outcome Ranking (DOOR) at OAV#1 or OAV#2

DOOR at OAV#1 is defined by ranking all subjects (pooling together both treatment arms) according to OCR at OAV#1 (lower is better) and using the number of days of antibiotic use at OAV#1 (lower is better) as a tie-breaker for comparing the ranking of two subjects with the same OCR. DOOR at OAV#2 is defined by ranking all subjects (pooling together both treatment arms) according to OCR at OAV#2 (lower is better) and using the number of days of antibiotic use at OAV#2 (lower is better) as a tie-breaker for comparing the ranking of two subjects with the same OCR. DOOR at OAV#1 or at OAV#2 is missing only if OCR or number of days of antibiotic use is missing for the respective OAV.

The ranking algorithm for DOOR is implemented as follows. A score variable is created that adds the number of days of antibiotic use (as defined in Section 6.5.6) divided by 100 to the OCR. Subjects are then ranked (DOOR) by the score, with the highest rank going to the subject with the lowest score, and the lowest rank going to the subject with the highest score. Tied scores result in a DOOR equal to the mean of the tied ranks. The algorithm is exemplified below using a simple scenario with 4 subjects.

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

6.6. Interim Analyses and Data Monitoring

One interim analysis, described below, will be performed by the SDCC statistician responsible for this protocol and reported to the DSMB after approximately 30% of the targeted subjects have completed the study. The interim analysis will inform DSMB decisions regarding stopping early for efficacy, futility, or safety. Only the SDCC statistician and the DSMB will see the interim analysis report.

For the interim analysis, a snapshot of the study database will be unblinded and used to conduct analyses as follows. An ITT analysis including all enrolled subjects in the snapshot of the study database will be performed, testing the null hypothesis (H0: Probability of higher DOOR in short course + ½ probability of equal DOOR = 0.5) using the methods described in Section 8.1.1, with the modification that the Haybittle-Peto boundary ($p<0.001$) will be used when concluding statistical significance. The study may be stopped early for efficacy only if statistical significance is detected in that test. In the event of statistical significance, sensitivity analyses using complete case and according-to-protocol cohorts (CC-V1 and ATP-V1, as described below) as well as worst case analyses will be included in the DSMB report to further guide decisions for stopping for efficacy.

A 95% confidence interval for the probability that a randomly selected subject will have a better DOOR if assigned to the 5-day strategy (vs. the standard strategy) will be estimated but not used to inform DSMB decisions about stopping early for efficacy. Predicted interval plots (PIPS, Section 6.6.1) will be constructed to provide the DSMB with a prediction of the trial results were the trial to continue as planned under varying assumptions regarding future data (e.g., current trend continues, null hypothesis is true, alternative hypothesis is true). In order to assess whether the 5-day strategy is differentially effective in subgroups of subjects, 95% confidence intervals for the probability of higher DOOR (as well as p-values for the test of a probability of higher DOOR of 0.5) when assigned to the short course of antibiotics will be shown as forest plots comparing each stratification variable (age <2 years, age ≥2 years, ED as the initial treatment site, out-patient or urgent care as the initial treatment site, amoxicillin as the initial antibiotic, amoxicillin-clavulanate as initial antibiotic, and cefdinir as initial antibiotic).

The DSMB will also be provided with the following:

1. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a between arm difference in the overall outcome (DOOR) via a cumulative difference plot with respective confidence bands for Outcome Assessment Visit #1.
2. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics at Outcome Assessment Visit #1.
3. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) Oral, rectal, axillary or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding Outcome Assessment Visit #1 or measured at the assessment visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia; (2) Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at Outcome Assessment Visit #1, and (3) Presence of cough Grade 2 or 3 at Outcome Assessment Visit #1.
4. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of each solicited event and with the risk difference of any solicited event, for each severity threshold (mild or greater, moderate or greater, or severe) for Outcome Assessment Visit #1.

The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

6.6.1. Predicted Interval Plots (PIPs)

PIPs provide insight into the range of possible outcomes that can be expected for the final primary analysis under various assumptions (such as that the current observed treatment effect

represents the true effect or that the null hypothesis represents the true effect). Using various assumptions, data is simulated from theoretical distributions to create multiple complete datasets representing complete datasets for the final analysis under the assumed reality. Details of PIPs and their interpretations can be found in the literature (Evans 2007, Li 2009).

For each assumption, one-hundred (100) 95% predicted intervals of the probability of higher DOOR in the 5-day treatment course at Outcome Assessment Visit #1 will be generated from 100 complete datasets. Each dataset will include the ITT analysis population for the interim analysis, plus additional simulated subjects to a total of 400 subjects in the dataset. Predicted intervals will be computed by inverting the Mann-Whitney U test (Section 8.2.2). The predicted intervals will be ordered by their corresponding point estimate of the probability of higher DOOR in the 5-day treatment course and shown graphically as forest plots. The 95% confidence interval generated in the ITT interim analysis of the probability of higher DOOR at Outcome Assessment Visit #1 will be overlaid on the forest plot. Comparisons of the predicted intervals to the confidence interval show changes in precision of estimated probability (tightness of predicted intervals versus the confidence interval) as well as the expected distribution of location shifts of the estimated probability in the final analysis relative to the interim analysis, dependent on the assumptions used. Conditional power will be estimated as the percentage of predicted intervals with a lower bound that is greater than 0.5.

Three assumptions will be included in the PIPs: 1) current trend, 2) null hypothesis, and 3) alternative hypothesis. Further assumptions may be explored depending on results of the ITT analysis of the primary endpoint, but will not be pre-specified.

Under the current trend assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the empirical distribution of DOOR values by treatment from the same dataset.

Under the null hypothesis assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the overall (not by treatment) empirical distribution of DOOR values from the same dataset.

Under the alternative hypothesis assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the overall

(not by treatment) empirical distribution of DOOR values from the same dataset. All simulated subjects with a treatment assignment randomly chosen as the 5-day course will have the DOOR (rank) shifted by a value beta. The value beta will be chosen through a manual trial-and-error process such that the probability of higher DOOR in the 5-day subjects, comparing simulated subjects only, has a mean value of approximately 0.6 across all 100 datasets.

6.7. Multicenter Studies

This is a multicenter study. Because there are twelve strata prior to considering site, further stratification by site would result in an excessive number of strata and so randomization is not stratified by site. Therefore, treatment imbalances might by chance occur within sites. Additionally, the potential for site effects on DOOR components is present. Therefore, sensitivity analyses for potential site effects are necessary.

In the primary analysis, data will be pooled across all clinical sites and analyses will not adjust for potential site effects. However, as a sensitivity analysis, the ITT analysis of DOOR at Outcome Assessment Visit #1 will be repeated as a stratified analysis in which each site will be analyzed separately (see Section 8.3.2).

6.8. Multiple Comparisons/Multiplicity

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

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Reasons for screening failures will be summarized in Table 8. The completion status and reasons for early termination or treatment discontinuation will be summarized (Table 4 and Listing 1). A subject could be discontinued early due to an AE (serious or non-serious), loss to follow-up, non-compliance with study, voluntary withdrawal by parent/guardian, withdrawal at the investigator request, termination of the site by the sponsor, termination of the study by the sponsor, death, lack of eligibility at enrollment, or becoming ineligible after enrollment.

Subject disposition and eligibility for analysis will be summarized in a CONSORT flow diagram (Figure 2).

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 2 and Listing 2). Non-subject specific protocol deviations will be in Listing 3. All subject-specific protocol deviations and non subject-specific protocol deviations will be presented. Major protocol deviations (see Section 6.3.3) will be discussed.

8. EFFICACY EVALUATION

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

All statistical tests are two-sided and performed at the α=0.05 significance level.

8.1. Primary Efficacy Analysis

The primary efficacy analyses will be performed for the ITT cohort.

8.1.1. Primary Analysis of DOOR at Outcome Assessment Visit #1

DOOR at Outcome Assessment Visit #1 is defined in Section 3.3.

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

> H0: The sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR at Outcome Assessment Visit #1 than if assigned to the 10-day arm plus one-half the probability of equal DOORs at Outcome Assessment Visit #1 is 50% (i.e., no difference in DOOR at Outcome Assessment Visit #1).

The above null hypothesis can be tested using a Mann-Whitney U Test (Evans 2015).

The primary analysis will use multiple imputation with a linear model to impute missing DOOR at Outcome Assessment Visit #1 outcomes. Details of multiple imputation methods are described in Section 8.4.1.

For each of the 20 complete multiply imputed datasets, a Mann-Whitney U statistic will be computed using randomization to short course versus randomization to standard course to define the binary grouping and DOOR at Outcome Assessment Visit #1 as the outcome. The U statistics are asymptotically normal distributed, and so they can be combined into a single test statistic using Rubin's Rules (Marshall 2009).

Defining the following:

n_1: number of subjects in ITT cohort randomized to a short course of antibiotics

n_2: number of subjects in ITT cohort randomized to a standard course of antibiotics

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

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

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

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

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

$$\bar{U} = \mathrm{Var}(Q_i) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \sum_{c=1}^{D}(M_c^3 - M_c)\right]$$ (Lehmann 1975, Zhao 2008),

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

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

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

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

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

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

Under null hypothesis corresponding to the primary analysis of this study,

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

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

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

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

A point estimate of the probability will be obtained by dividing $\bar{Q}$ by $n_1 n_2$. Results will be shown in Table 14.

8.2. Secondary Efficacy Analyses

8.2.1. Analysis of DOOR at Outcome Assessment Visit #2, Performed as ITT in an Analogous Manner to the Primary Analysis

DOOR at Outcome Assessment Visit #2 is defined in Section 3.3.

The null hypothesis corresponding to this analysis is:

> H0: The sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR at Outcome Assessment Visit #2 than if assigned to the 10-day arm plus one-half the probability of equal DOORs at Outcome Assessment Visit #2 is 50% (i.e., no difference in DOOR at Outcome Assessment Visit #2).

The above null hypothesis can be tested using a Mann-Whitney U Test (Evans 2015).

This analysis will use multiple imputation with a linear model to impute missing DOOR at Outcome Assessment Visit #2 outcomes. Details of multiple imputation methods are described in Section 8.4.1.

For each of the 20 complete multiple imputation datasets, a Mann-Whitney U statistic will be computed using randomization to short course versus randomization to standard course to define the binary grouping and DOOR at Outcome Assessment Visit #2 as the outcome. The U statistics are asymptotically normal distributed, and so they can be combined into a single test statistic using Rubin's Rules (Marshall 2009).

Defining the following:

n_1: number of subjects in ITT cohort randomized to a short course of antibiotics

n_2: number of subjects in ITT cohort randomized to a standard course of antibiotics

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

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

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

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

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

$$\bar{U} = \text{Var}(Q_i) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \sum_{c=1}^{D}(M_c^3 - M_c)\right]$$ (Lehmann 1975, Zhao 2008),

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

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

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

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

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

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

Under null hypothesis corresponding to the primary analysis of this study,

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

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

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

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

A point estimate of the probability will be obtained by dividing $\bar{Q}$ by $n_1 n_2$. Results will be shown in Table 15.

8.2.2. Sensitivity Analyses for the DOOR at Outcome Assessment Visits #1 and #2 ITT analyses.

In addition to the ITT analysis of the DOOR at Outcome Assessment Visits #1 and #2, analyses using alternative analysis populations or imputation strategies will be performed: (1) CC analyses. (2) ATP analyses. (3) Worst case analyses. All of these analyses will test the null hypotheses described in Section 8.1.1 and Section 8.2.1 using the Mann-Whitney U Test, estimate Pr(Higher DOOR in short course) + 0.5 Pr(Equal DOOR) using U divided by the number of pairwise comparisons, and will compute confidence intervals by (1) inverting the Mann-Whitney U Test and (2) using a non-parametric bootstrap. Results will be shown in Table 16 and Table 17 for Outcome Assessment Visits #1 and #2, respectively.

Confidence intervals from inverting the Mann-Whitney U Test:

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

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

$$\mathrm{Var}(U) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \sum_{c=1}^{D}(M_c^3 - M_c)\right] \quad \text{(Lehmann 1975, Zhao 2008),}$$

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

Confidence intervals using a non-parametric bootstrap:

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

Where $U_{0.025}$ and $U_{0.975}$ are chosen as the 250th and 9750th values in a sorted array of 10,000 values of Mann Whitney U statistics generated from random resampling (number of values sampled to generate the statistic will be equal to the number of subjects in the respective analysis population) of the empirical distributions of DOOR scores in each treatment arm for the given analysis population.

8.2.2.1. Complete Case Analysis of the DOOR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.2 using the CC-V1 population. Ordinal clinical response values, number of days of antibiotic use, and DOOR at outcome assessment visit #1 of CC-V1 subjects will be presented in Listing 19.

8.2.2.2. Complete Case Analysis of the DOOR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.2 using the CC-V2 population. Ordinal clinical response values, number of days of antibiotic use, and DOOR at outcome assessment visit #2 of CC-V2 subjects will be presented in Listing 19.

8.2.2.3. According-to-Protocol Analysis of the DOOR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.2 using the ATP-V1 population.

8.2.2.4. According-to-Protocol Analysis of the DOOR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.2 using the ATP-V2 population.

8.2.2.5. Worst Case Analysis of the DOOR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.2 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8 and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 0. As an exception, subjects in the short course arm with OCR missing for Outcome Assessment Visit #1 but not for Outcome Assessment Visit #2 will have the OCR for Outcome Assessment Visit #1 imputed as the Outcome Assessment Visit #2 value or as 5,

whichever value is larger. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.) and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 5.

8.2.2.6. Worst Case Analysis of the DOOR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.2 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8 and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 0. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.) and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 5.

8.2.3. Solicited Events at Outcomes Assessment Visits #1 and #2

Separately for Outcome Assessment Visit #1 and #2, using CC-V1 and CC-V2, respectively, a forest plot of 95% confidence intervals for the risk difference of each solicited event and the risk difference of any solicited, for each severity threshold (mild or greater, moderate or greater, or severe) will be produced (Figure 3, Figure 4, Figure 5 and Figure 6, Figure 7, Figure 8). Results will also be reported in tables (Table 18, Table 19, Table 20, Table 21, Table 22, and Table 23), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

8.2.4. Resolution of Symptoms at Outcomes Assessment Visits #1 and #2

Separately for Outcome Assessment Visit #1 and #2, using CC-V1 and CC-V2, respectively, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) fever (as defined in Section 6.5.2) (2) Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit; and (3) Presence of cough Grade 2 or 3 at the Outcome Assessment Visit will be given (Figure 9 and Figure 10). Results will also be reported in tables (Table 24 and Table 25), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

8.2.5. Adequate Clinical Response at Outcomes Assessment Visits #1 and #2

Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics will be given (Figure 11 and Figure 13). Results will also be reported in tables (Table 26 and Table 28), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of the following interventions for any reason: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics will be given (Figure 12 and Figure 14). Results will also be reported in tables (Table 27 and Table 29), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

8.2.6. Ordinal Clinical Response at Outcomes Assessment Visits #1 and #2

Analysis of the ordinal clinical response (OCR) at Outcome Assessment Visits #1 and #2. Separately for OCR at each of the two visits, a first ITT analysis (superiority/inferiority) will test the null hypothesis that

$$\Pr(\text{OCR is better in short course}) + 0.5 \Pr(\text{OCR is equal}) = 0.5.$$

A second ITT analysis (non-inferiority) will test the null hypothesis that

$$\Pr(\text{OCR is better in short course}) + 0.5 \Pr(\text{OCR is equal}) < 0.4.$$

ITT, CC, ATP, and worst case analyses will plot cumulative difference plots and test whether the overall distributions of OCR are equivalent between the treatment arms for OCR at each of the two visits.

Cumulative difference plots (Figure 15, Figure 16, Figure 17, Figure 18 and Figure 19, Figure 20, Figure 21, Figure 22) are produced as follows. For $i \in \{1,2,3,4,5,6,7\}$, the difference in proportions of subjects with $\text{OCR} \leq i$ between treatment arms is plotted (i on x-axis and difference in proportion on y-axis), together with 95% confidence intervals computed using the Newcombe method with continuity correction.

For CC-V1, CC-V2, ATP-V1, and ATP-V2 analysis populations, OCRs will be summarized by treatment group and tests of overall distributions of OCR will be performed using the mean score statistic (QS). The mean score statistic is obtained from PROC FREQ in SAS using the "chisq" option and is denoted in output as the "Mantel-Haenszel Chi-Square" statistic.

8.2.6.1. ITT Analyses of OCR at Outcomes Assessment Visit #1

Twenty (20) multiple imputation datasets for OCR at Outcome Assessment Visit #1 will be generated in manner analogous to that described in Section 8.1.1, except using OCR at Outcome Assessment Visit #1 in place of DOOR at Outcome Assessment Visit #1 for the response. Also, analogous to Section 8.1.1, the Mann-Whitney U statistic will be computed for each of the datasets and combined using Rubin's Rules to generate the test statistic W and a p-value for the test of the null hypothesis that

$$\Pr(\text{OCR at Outcome Assessment Visit \#1 is better in short course}) + 0.5 \Pr(\text{OCR at Outcome Assessment Visit \#1 is equal}) = 0.5.$$

The F-test using the W statistic will be inverted to produce a 95% confidence interval for Pr(OCR is better in short course) + 0.5 Pr(OCR is equal). Whether the lower bound of this confidence interval is greater than 0.4 will serve as a test of the non-inferiority null hypothesis that

Pr(OCR at Outcome Assessment Visit #1 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) < 0.40.

Results will be reported in Table 30.

8.2.6.2. ITT Analyses of OCR at Outcomes Assessment Visit #2

Twenty (20) multiple imputation datasets for OCR at Outcome Assessment Visit #2 will be generated in manner analogous to that described in 8.2.1, except using OCR at Outcome Assessment Visit #2 in place of DOOR at Outcome Assessment Visit #2 for the response. Also, analogous to 8.2.1, the Mann-Whitney U statistic will be computed for each of the datasets and combined using Rubin's Rules to generate the test statistic W and a p-value for the test of the null hypothesis that

Pr(OCR at Outcome Assessment Visit #2 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5.

The F-test using the W statistic will be inverted to produce a 95% confidence interval for Pr(OCR is better in short course) + 0.5 Pr(OCR is equal). Whether the lower bound of this confidence interval is greater than 0.4 will serve as a test of the non-inferiority null hypothesis that

Pr(OCR at Outcome Assessment Visit #2 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) < 0.40.

Results will be reported in Table 31.

8.2.6.3. Complete Case Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the CC-V1 population. Results will be reported in Table 32 and Table 33.

8.2.6.4. Complete Case Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the CC-V2 population. Results will be reported in Table 34 and Table 35.

8.2.6.5. According-to-Protocol Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the ATP-V1 population. Results will be reported in Table 36 and Table 37.

8.2.6.6. According-to-Protocol Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the ATP-V2 population. Results will be reported in Table 38 and Table 39.

8.2.6.7. Worst Case Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8. As an exception, subjects in the shorts course arm with OCR missing for Outcome Assessment Visit #1 but not for Outcome Assessment Visit #2 will have the OCR for

Outcome Assessment Visit #1 imputed as the Outcome Assessment Visit #2 value or as 5, whichever value is larger. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.). Results will be reported in Table 40.

8.2.6.8. Worst Case Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.). Results will be reported in Table 41.

8.2.7. Additional Analysis of Cough

The proportion of subjects in each treatment group experiencing moderate or severe cough will be tabulated by day from Day 1 to Day 25 (as recorded from the memory aid), by visit, and overall, with 95% exact confidence intervals (Table 42). The proportion of subjects in each treatment group experiencing cough will also be tabulated by day from Day 1 to Day 25 (as recorded from the memory aid), by visit, and by severity level (Table 43 and Table 44). Finally, cough will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) (Table 45). Proportions for these derived binary variables will be reported along with 95% exact confidence intervals. Comparisons of proportions by treatment groups will be given as odds ratios (with 95% exact confidence intervals) and p-values from Fisher's Exact Tests. Cough severity will be listed by study day and study visit (Listing 15 and Listing 16).

8.3. Exploratory Efficacy Analyses

8.3.1. Complete Case Evaluation of DOOR at Outcome Assessment Visit #1, Minimum Required Difference in Days for Antibiotic Use "Tie-breaking" Varies k=1,2,3,4,5, or infinity

In the primary RADAR/DOOR analysis, if two subjects from separate treatment arms have an equal ordinal clinical response but a difference in the duration of antibiotic use of at least k=1 day, RADAR assigns a more favorable response to the subject with fewer days of antibiotic use. For a sensitivity analysis, the effect of increasing the minimum difference in the duration of antibiotic use (k=2,3,4, or 5, or infinity) before a favorable response is given to the subject with shorter duration of antibiotic use will be explored. The analysis of RADAR/DOOR with k=infinity is equivalent to comparison of OCR without regard for number of days of antibiotic use, and is included here for comparative purposes. For each value of k, bootstrapped confidence intervals of the probability of more favorable DOOR due to assignment to the 5-day antibiotic course will be computed and plotted versus k. Analysis will be performed separately for DOOR at Outcome Assessment Visit #1 and DOOR at Outcome Assessment Visit #2. Analyses will be performed using CC-V1/CC-V2 cohorts. Results will be reported in Table 46 and Figure 23.

8.3.2. Stratified (ITT) Analyses of DOOR at Outcome Assessment Visit #1

Analysis of DOOR at Outcome Assessment Visit #1 as described in Section 8.1.1 will be performed separately for each level of each stratification variable (e.g. an analysis of all subjects of age <24 months at enrollment, and a separate analysis of all subjects of age 24-71 months at enrollment) and by clinical site. Results will be reported Table 47.

8.3.3. As Treated Analysis of Effect of Number of Days of Antibiotic Use on OCR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

The analysis will be performed using the subset of the CC-V1 analysis population that did not receive off-study systemic antibiotic unrelated to pneumonia prior to Outcome Assessment Visit #1. The justification for excluding subjects with unrelated antibiotic use is that subjects receiving unrelated antibiotics are at risk for both improved outcomes due to ongoing antibiotic use as well as increased side effects related to antibiotics administration. The effect of the number of days of antibiotic use at Outcome Assessment Visit #1 on OCR at Outcome Assessment Visit #1 will be analyzed using a proportional odds model that simultaneously uses all cumulative logits (Agresti 2003).

Let **K** be the set of distinct OCR values observed at Outcome Assessment Visit #1, with the exception that the highest (worst) distinct value observed is not included in the set.

Let Y_i = the OCR of subject i at Outcome Assessment Visit #1.

Let X_i = the number of days of antibiotic use at Outcome Assessment Visit #1 for subject *i*.

α_k, where $k \in K$, and β are parameters to be simultaneously estimated through maximum likelihood methods.

Then, proportional odds model with cumulative logits is defined as

$$\text{Logit}\,[P(Y_i > k)] = \alpha_k + \beta X_i , \qquad k \in \mathbf{K}$$

The following gives the interpretation of the model. Suppose D is any non-negative integer.

Then, $\log[\text{odds}(OCR>k \mid X_i = D+1) / \text{odds}(OCR>k \mid X_i = D)] = \beta$.

That is, for any *k*, where *k* is from the set of observed OCR values at Outcome Assessment Visit #1 besides the highest observed value, e^{β} gives the odds ratio of an OCR at Outcome Assessment Visit #1 greater than *k* for the effect of one additional day of use of antibiotic.

It should be stated clearly that this analysis is "as treated" rather than "as randomized." As such, causality cannot be inferred from a statistically significant association. This is especially true if subjects receiving off-study antibiotic not unrelated to the prior diagnosis of pneumonia are observed during the study. Such subjects will have a higher OCR and will also likely have more days of antibiotic use.

This analysis will be repeated using the subset of the CC-V2 analysis population that did not receive off-study systemic antibiotic unrelated to pneumonia prior to Outcome Assessment Visit #2. The effect of the number of days of antibiotic use at Outcome Assessment Visit #2 on OCR at Outcome Assessment Visit #2 will be analyzed using logistic regression with a proportional odds assumption. Results from both analyses will be summarized in Table 48. The odds ratio for the proportional odds of an OCR at Outcome Assessment Visit #1 greater than k for the effect of

one additional day of use of antibiotic will be reported with a 95% Wald confidence interval and p-value from a Wald test. For $p<0.05$, an association between OCR and the number of days of antibiotic use, as treated, will be concluded.

8.4. Imputation of Missing Data

8.4.1. Multiple Imputation of Missing Ordinal Clinical Response and DOOR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

Several analyses, including the primary analysis, depend on multiple imputation of DOOR or OCR at Outcome Assessment Visit #1 or Outcome Assessment Visit #2. Multiple imputations of each of these missing endpoints will be performed independently, and each subject will have their missing endpoints imputed independently of other subject's imputations using a subject-specific imputation model.

As a first step to multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for DOOR at Outcome Assessment Visit #1 and OCR at Outcome Assessment Visit #1 is below.

- Indicator of subject enrolled at the site with the second most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the third most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the least number of subjects enrolled (binary indicator)
    - Note: the site with the most number of subjects enrolled is reference for site. Language is written to allow for an arbitrary number of sites. In the event of a number of ties for the number of subjects enrolled, tied sites will be ordered in ascending alphanumeric order in the list of model variables.
- Indicator of amoxicillin (not amoxicillin placebo) as study treatment (binary indicator)
- Indicator of amoxicillin-clavulanate (not amoxicillin-clavulanate placebo) as study treatment (binary indicator)
- Indicator of cefdinir (not cefdinir placebo) as study treatment (binary indicator)
    - Note: placebo is the reference group for study treatment
- Indicator for amoxicillin-clavulanate as initial antibiotic (binary indicator)
- Indicator for cefdinir as initial antibiotic (binary indicator)
    - Note: amoxicillin is the reference group for initial antibiotic
- Indicator for age $\geq$ 2 years at enrollment (binary indicator)
- Indicator for initial treatment site for pneumonia at an emergency department (binary indicator)

- OCR at Outcome Assessment Visit #2 (imputed OCRs will not be used)
- Severity of cough on Day 1 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 1 (0, 1, 2, or 3)
- Severity of cough on Day 2 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 2 (0, 1, 2, or 3)
- Severity of cough on Day 3 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 3 (0, 1, 2, or 3)
- Severity of cough on Day 4 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 4 (0, 1, 2, or 3)
- Severity of cough on Day 5 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 5 (0, 1, 2, or 3)

For DOOR and OCR at Outcome Assessment Visit #2, the complete list of model variables is identical to the above, but with OCR at Outcome Assessment Visit #2 replaced with OCR at Outcome Assessment Visit #1. Additionally, cough severity and most severe solicited event are listed up to Day 18 rather than Day 5.

The actual list of model variables for each subject-specific imputation model will follow the ordering above, but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification given in the pseudo-code and subjects must be processed in the order described in the pseudo-code. OCR will simultaneously be imputed with DOOR at each respective Outcome Assessment Visit. The pseudo-code is in terms of the Outcome Assessment Visit #1 endpoints, but the general logic is also applicable to the Outcome Assessment Visit #2 endpoints (with references to "V1" replaces with references to "V2").

```
DEFINE i=index variable for subjects having DOOR imputed.
      Subjects requiring imputation are sorted in ascending order
      by PATID.
DEFINE N=number of subjects requiring imputation
DEFINE g&i=analysis dataset containing predictors and DOOR for
       CC-V1 subjects as well as subject i (only one subject not in
       CC-V1 included).  Note that CC-V1 subjects that are missing a
       value
       for one or more variables in the subject-specific imputation
       model are excluded.
DEFINE imp_g&i = g&i, with 20 imputed values for the missing DOOR
      added by PROC MI
DEFINE &&modelVars_&i  = list of observed variables in subject i, to
```

```
      be used for imputation of DOOR and OCR.

%do i=1 %to &N;
PROC MI data=g&i out=imp_g&i seed=1200&i NIMPUTE=20 noprint;
      var &&modelVars_&i DOOR OCR;
      monotone reg(DOOR_V1 = &&modelVars_&i);
      monotone reg(OCR_V1 = &&modelVars_&i);
run;
%end;

imp_g&i will be subset to contain only rows for the subjects with
imputed DOOR and merged together and with CC-V1 data to create the
twenty complete multiply imputed datasets
**********************************************************************
```

9. SAFETY EVALUATION

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

9.1. Demographic and Other Baseline Characteristics

Summaries of age, gender, enrollment site, ethnicity, race, initial antibiotic therapy, initial treatment locations, and age group (<24 months vs. 24-71 months) will be presented by site (Table 9 and Table 10) or by treatment group and overall (Table 11 and Table 12). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, a subject's guardians may designate the subject as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Summaries of subject's medical history will be presented by MedDRA® system organ class (SOC) and treatment group (Table 13).

Individual subject listings for all demographics (Listing 5) and pre-existing medical conditions (Listing 6) will be presented.

9.1.1. Concurrent Illnesses and Medical Conditions

Physical assessment findings from the enrollment visit, and any follow up visits, will be included in Listing 11.

9.1.2. Prior and Concurrent Medications

All concomitant medications taken within 30 days of signing the informed consent or during the study period will be recorded. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. A by-subject listing of concomitant medication use will be presented (Listing 12). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group (Table 55).

9.2. Measurements of Treatment Compliance

Treatment was administered to subjects at their homes by a parent or caregiver. The number of subjects receiving the first dose of study product will be tabulated by site, treatment group, and time period (Table 6). The number of doses of study product administered will be presented by treatment group (Table 7, Listing 7).

9.3. Adverse Events

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

9.3.1. Solicited Events

Solicited events will be captured daily until Outcome Assessment Visit #1; thereafter, parents/legal guardians will report symptoms based on memory aid and medical interview by study staff. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Solicited events were recorded for trial Days 1-25, or until study completion or termination, as the maximum severity for each day. Target solicited events include irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis.

The proportion of subjects in each treatment group experiencing each solicited event with mild or greater severity will be tabulated by day and overall (Table 49). The proportion of subjects in each treatment group experiencing each solicited event will also be tabulated by day and severity level (Table 50). Finally, solicited events will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) (Table 52). Proportions for these derived binary variables will be reported along with 95% exact confidence intervals. Comparisons of proportions by treatment groups will be given as odds ratios (with 95% exact confidence intervals) and p-values from Fisher's Exact Tests.

The maximum severity occurrence of each solicited event and cough (proportion of subjects for each severity level) will be plotted for each solicited adverse event (Figure 24). Solicited events by subject will also be presented (Listing 8).

9.3.2. Unsolicited Adverse Events

As the safety profile of amoxicillin, amoxicillin-clavulanate, and cefdinir are well established, and this trial is not powered to detect new, unknown safety signals, **there will be no unsolicited event collection during this study and only protocol-defined SAE's will be collected**.

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

Detailed narratives will be given for any deaths or other protocol-defined SAEs that occurred during the study. Listings of SAEs will be presented including subject ID, AE description, AE onset date/end date, reason reported as an SAE, relationship to treatment, alternate etiology if not related, outcome, and duration of event (days) (Listing 9). SAEs will also be listed in Table 53.

9.5. Vital Signs and Physical Evaluations

Vital signs will be taken at the enrollment visit, Outcome Assessment Visit #1, and Outcome Assessment Visit #2. For each visit, by treatment group, the mean, median, standard deviation, min, and max of vital sign will be calculated for temperature, respiration rate, and pulse (Table 54). Individual vital signs measurements will be listed (Listing 10).

9.6. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be

presented. The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the Safety population (Table 55).

9.7. Other Safety Measures

The number and percent of subjects visiting an emergency department, primary care provider, study physician, urgent care, or having some other type of medically attended visit due to worsening study pneumonia will be presented together with whether the subject received antibiotic, surgical treatment, or was hospitalized due to pneumonia or a complication of pneumonia (Table 56). Medically attended visits will also be listed (Listing 13 and Listing 14). Presence of fever will be listed by visit (Listing 17 and Listing 18).

10. OTHER ANALYSES

No other analyses are planned.

11. REPORTING CONVENTIONS

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

12. TECHNICAL DETAILS

SAS version 9.3 or above or R version 3.2 or above will be used to perform analyses and to generate all tables, figures and listings.

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

Changes in the Conduct of the Study

Enrollment into the study was initiated under protocol version 2.0. Substantive changes to the protocol after study initiation are provided below.

Substantive changes in protocol version 3.0

- Removed 200mg/5mL amoxicillin and 200mg/5mL amoxicillin-clavulanate as possible dose strengths under Protocol Section 6.1.2. No subjects were prescribed under this dose.
- Clarified timing of interim analysis to be after at least 30% of the targeted subjects have completed the study instead of approximately 30%.

Changes to the Planned Analyses

There are no changes to the planned analyses as described in the protocol.

14. REFERENCES

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15. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

10.2 Protocol Deviations

Table 2: Distribution of Protocol Deviations by Category, Type and Treatment Group

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

12.2.2 Displays of Adverse Events

Table 3: Solicited Adverse Event Grading Scale

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Irritability	More irritable or fussy than usual but can be consoled; no interference with smiling/playing	Irritability or fussiness that is difficult to console and interferes with smiling and playing	Irritability or fussiness that lasts for more than 4 consecutive hours in a 24 hour period or cannot be consoled
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 occurring >6 times/day	Bloody diarrhea, or diarrhea that requires medical intervention, laboratory testing, or hospitalization
Allergic Reaction	Localized rash or pruritus without rash	Diffuse rash (maculopapular or urticarial)	Generalized rash consistent with Stevens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis; anaphylaxis; or angioedema
Stomatitis	Oral lesions associated with parenteral report of mild oral discomfort	Oral lesions associated with difficulty swallowing, but able to eat and drink	Oral lesions associated with inability to swallow solids or liquids; requires medical intervention, IV fluids, or hospitalization
Candidiasis	Mild mucocutaneous candidiasis or diaper dermatitis, with no treatment or topical treatment only	Moderate mucocutaneous candidiasis requiring oral antimicrobial treatment	Severe mucocutaneous candidiasis; requires medical intervention, intravenous treatment, or hospitalization

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 4: Subject Disposition by Treatment Group

Subject Disposition	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received First Dose of Treatment	x	xx	x	xx	x	xx
Received All Scheduled Treatment[a]	x	xx	x	xx	x	xx
Completed Completed All Future Use Sample Collection						
Completed Outcome Assessment Visit #1 (Study Day 6-10)[a]						
Completed Outcome Assessment Visit #2 (Study Day 19-25) [a]						

[a] Refer to Listing 1 for reasons subjects discontinued or terminated early.
[b] Refer to Listing 4 for reasons subjects are excluded from the Analysis populations.

Table 5: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
ITT[1]	Any Reason	x	xx	x	xx	x	xx
CC-V1[2]	Any Reason						
	Subject not treated with study product						
	Early termination before Outcome Assessment Visit #1						
	-Reason 1 for termination						
	-Reason 2 for termination						
	Completed Outcome Assessment Visit #1, but Missing DOOR Component						
	-Adequate Clinical Response						
	-Resolution of Symptoms						
	-Solicited Event Severity Days 1-5						
	-Number of Days of Antibiotic Use						
CC-V2	Any Reason						
	Subject not treated with study product						
	Early termination before Outcome Assessment Visit #2						
	-Reason 1 for termination						
	-Reason 2 for termination						
	Completed Outcome Assessment Visit #2, but Missing DOOR Component						
	-Adequate Clinical Response						
	-Resolution of Symptoms						
	-Solicited Event Severity Days 1-8						
	-Number of Days of Antibiotic Use						
ATP-V1[3]	Any Reason						
	The subject was excluded from CC-V1 cohort.						
	Subject did not receive at least one dose of study product each day from Day 1 to Day 5						
	Major protocol deviation						

Table 5: Analysis Populations by Treatment Group *(continued)*

Analysis Populations	Reason Subjects Excluded	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
	-Deviation Type 1						
	-Deviation Type 2						
ATP-V2	Any Reason						
	The subject was excluded from CC-V2 cohort.						
	Subject did not receive at least one dose of study product each day from Day 1 to Day 5						
	Major protocol deviation						
	-Deviation Type 1						
	-Deviation Type 2						

[1] ITT = Intent-to-Treat
[2] CC = Complete Case
[3] ATP = According-to-Protocol

Table 6: Dates of First Treatment by Site and Treatment Group

Site	Treatment Group	July 2016 - June 2017	July 2017 - June 2018	July 2018 - June 2019
Children's Hospital of Philadelphia	Standard Course	x	x	x
	Short Course	x	x	x
Children's Hospital of Pittsburgh	Standard Course	x	x	x
	Short Course	x	x	x
Cincinnati Children's Hospital	Standard Course	x	x	x
	Short Course	x	x	x
Duke University	Standard Course	x	x	x
	Short Course	x	x	x
Vanderbilt University	Standard Course	x	x	x
	Short Course	x	x	x
Any Site	Standard Course	x	x	x
	Short Course	x	x	x
Any	Any	x	x	x

[Programming Note: Rows will be added for additional sites that enroll at least one subject, as needed.]

Table 7: Treatment Compliance by Treatment Group

	Number of Doses Administered n (%)												
Treatment Group	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Standard Course (N=X)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Short Course (N=X)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 8: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible[1]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x
Inclusion	Any inclusion criterion	x
	[inclusion criterion 1]	x
	[inclusion criterion 2]	x
	[inclusion criterion 3]	x
Exclusion	Any exclusion criterion	x
	[exclusion criterion 1]	x
	[exclusion criterion 2]	x
	[exclusion criterion 3]	x

[1] More than one criterion may be marked per subject.

14.1.2 Demographic Data by Study Group

Table 9: Summary of Categorical Demographic and Baseline Characteristics by Site

Demographic Category	Characteristic	Children's Hospital of Philadelphia (N=X)		Children's Hospital of Pittsburgh (N=X)		Cincinnati Children's Hospital (N=X)		Duke University (N=X)		Vanderbilt University (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Initial Antibiotic	Amoxicillin	x	x	x	x	x	x	x	x	x	x	x	x
	Amoxicillin-Clavulunate	x	x	x	x	x	x	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x	x	x	x	x	x	x

[Programming Note: Columns will be added for additional sites that enroll at least one subject, as needed.]

Table 10: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	Children's Hospital of Philadelphia (N=X)	Children's Hospital of Pittsburgh (N=X)	Cincinnati Children's Hospital (N=X)	Duke University (N=X)	Vanderbilt University (N=X)	All Subjects (N=X)
Age (Months)	Mean	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x

[Programming Note: Columns will be added for additional sites that enroll at least one subject, as needed.]

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Demographic Category	Characteristic	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x
	Female	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Initial Antibiotic	Amoxicillin	x	x	x	x	x	x
	Amoxicillin-Clavulunate	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x
Clinical Trial Site	Children's Hospital of Philadelphia	x	x	x	x	x	x
	Children's Hospital of Pittsburgh	x	x	x	x	x	x
	Cincinnati Children's Hospital	x	x	x	x	x	x
	Duke University	x	x	x	x	x	x
	Vanderbilt University	x	x	x	x	x	x

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Statistic	Standard Course (N=X)	Short Course (N=X)	All Subjects (N=X)
Age	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

14.1.3 Prior and Concurrent Medical Conditions

Table 13: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

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

Note: N=Number of subjects enrolled; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy/Immunogenicity Data

Table 14: Primary ITT Analysis of DOOR at Outcome Assessment Visit #1

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx

1 Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR. Confidence interval obtained through inversion of the F-test used to compute the p-value.
2 P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 15: Primary ITT Analysis of DOOR at Outcome Assessment Visit #2

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx

1 Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal DOOR. Confidence interval obtained through inversion of the F-test used to compute the p-value.
2 P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 16: Sensitivity Analyses of DOOR at Outcome Assessment Visit #1

Analysis	Pr(Higher DOOR)[1]	Normal Approx. 95% CI[2]	Bootstrapped 95% CI[3]	P-value[4]
Complete Case (CC-V1)				
According-to-Protocol (ATP-V1)				
Worst Case (ITT)				

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR.
[2] Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance Var(U)=n1n2(n1+n2+1)/12.
[3] 2.5th and 97.5th percentiles of Pr(Higher DOOR) obtained by repeatedly re-sampling of the empirical distributions of DOOR scores by treatment arm.
[4] P-value obtained by Mann-Whitney U Test.

Table 17: Sensitivity Analyses of DOOR at Outcome Assessment Visit #2

Analysis	Pr(Higher DOOR)[1]	Normal Approx. 95% CI[2]	Bootstrapped 95% CI[3]	P-value[4]
Complete Case (CC-V2)				
According-to-Protocol (ATP-V2)				
Worst Case (ITT)				

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal DOOR.
[2] Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance Var(U)=n1n2(n1+n2+1)/12.
[3] 2.5th and 97.5th percentiles of Pr(Higher DOOR) obtained by repeatedly re-sampling of the empirical distributions of DOOR scores by treatment arm.
[4] P-value obtained by Mann-Whitney U Test.

Table 18: Risk of Mild, Moderate, or Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 19: Risk of Moderate or Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 20: Risk of Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 21: Risk of Mild, Moderate, or Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 22: Risk of Moderate or Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 23: Risk of Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 24: Lack of Resolution of Symptoms and Its Components at Outcome Assessment Visit #1 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Resolution of Symptoms									
Fever[2]									
Elevated respiratory rate[3]									
Cough[4]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of fever, elevated respiratory rate, and cough at Outcome Assessment Visit #1.

[1] P-value obtained by Fisher Exact Test.

[2] As defined in Section 6.5.2 of the SAP.

[3] Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit.

[4] Presence of cough Grade 2 or 3 at the Outcome Assessment Visit.

Table 25: Lack of Resolution of Symptoms and Its Components at Outcome Assessment Visit #2 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Resolution of Symptoms									
Fever[2]									
Elevated respiratory rate[3]									
Cough[4]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of fever, elevated respiratory rate, and cough at Outcome Assessment Visit #2.

[1] P-value obtained by Fisher Exact Test.

[2] As defined in Section 6.5.2 of the SAP.

[3] Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit.

[4] Presence of cough Grade 2 or 3 at the Outcome Assessment Visit.

Table 26: Risk of Lack of Adequate Clinical Response and Its Components from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Adequate Clinical Response									
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[3]									
Receipt of Non-Study Antibiotic[4]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
[3] For pneumonia or treatment for a complication of pneumonia, including but not limited to drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
[4] For pneumonia or treatment for a complication of pneumonia. Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

Table 27: Any Receipt of Non-Study Antibiotics and Medically Attended Visits from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[2]									
Receipt of Non-Study Antibiotic[2]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For any reason.

Table 28: Risk of Lack of Adequate Clinical Response and Its Components from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Adequate Clinical Response									
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[3]									
Receipt of Non-Study Antibiotic[4]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
[3] For pneumonia or treatment for a complication of pneumonia, including but not limited to drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
[4] For pneumonia or treatment for a complication of pneumonia. Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

Table 29: Any Receipt of Non-Study Antibiotics or Medically Attended Visit from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[2]									
Receipt of Non-Study Antibiotic[2]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For any reason.

Table 30: ITT Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 31: ITT Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 32: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (CC-V1)

Statistic	Value
CC-V1 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 33: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (CC-V1) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 34: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (CC-V2)

Statistic	Value
CC-V2 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.

[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.

[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 35: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (CC-V2) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 36: According-to-Protocol Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ATP-V1)

Statistic	Value
ATP-V1 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
Test No Difference in OCR, P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.

[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.

[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 37: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ATP-V1) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 38: According-to-Protocol Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ATP-V2)

Statistic	Value
ATP-V2 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 39: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ATP-V2) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 40: Worst Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ITT Cohort)

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
Test No Difference in OCR, P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 41: Worst Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ITT Cohort)

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.

[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.

[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 42: Number and Percentage of Subjects Experiencing Moderate or Severe Cough by Day and Treatment Group

	Standard Course - Moderate or Severe Cough				Short Course - Moderate or Severe Cough			
Study Day or Visit	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Overall	x	x	x	(x, x)	x	x	x	(x, x)
OAV #1	x	x	x	(x, x)	x	x	x	(x, x)
OAV #2	x	x	x	(x, x)	x	x	x	(x, x)
Day 1	x	x	x	(x, x)	x	x	x	(x, x)
Day 2	x	x	x	(x, x)	x	x	x	(x, x)
Day 3	x	x	x	(x, x)	x	x	x	(x, x)
Day 4	x	x	x	(x, x)	x	x	x	(x, x)
Day 5	x	x	x	(x, x)	x	x	x	(x, x)
Days 6-9	x	x	x	(x, x)	x	x	x	(x, x)
Day 10-13	x	x	x	(x, x)	x	x	x	(x, x)
Day 14-18	x	x	x	(x, x)	x	x	x	(x, x)
Day 19-25	x	x	x	(x, x)	x	x	x	(x, x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 43: Number and Percentage of Subjects Experiencing Coughing by Maximum Severity and Treatment Group – Standard Course

Severity	Standard Course								
	Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 44: Number and Percentage of Subjects Experiencing Coughing by Maximum Severity and Treatment Group – Short Course

Severity	Short Course								
	Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 45: Number and Percentage of Subjects Experiencing Cough of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group

Severity	Standard Course (N=X)		Short Course (N=X)		Odds Ratio (95% CI)	P-Value
	n (%)	95% CI	n (%)	95% CI		
Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

Table 46: CC-V1 Evaluation of DOOR at Outcome Assessment Visit #1, Minimum Required Difference in Days for Antibiotic Use "Tie-Breaking" Varies k=1,2,3,4,5, or Infinity

k	Pr(Higher DOOR)[1]	95% CI	P-value
1	x.x	(x.x – x.x)	x.x
2			
3			
4			
5			
∞			

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR

Table 47: ITT Evaluation of DOOR at Outcome Assessment Visit #1, Analysis By Stratification Variable and Clinical Site

Variable	Level	Pr(Higher DOOR)[1]	95% CI	P-value
Age (Months)	<24	x.x	(x.x – x.x)	x.x
	24-71			
Initial Site of Treatment	ED			
	Out-Patient / Urgent Care			
Initial Antibiotic	Cefdinir			
	Amoxicillin			
	Amoxicillin Clavulanate			
Clinical Site	Children's Hospital of Philadelphia			
	Children's Hospital of Pittsburgh			
	Cincinnati Children's Hospital			
	Duke University			
	Vanderbilt University			

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR

[Programming Note: Rows will be added for additional sites that enroll at least one subject, as needed.]

Table 48: As Treated Analysis of Association between Ordinal Clinical Response and the Number of Days of Antibiotic Use at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

Outcome Assessment Visit[1]	Proportional Odds[2] Odds Ratio for 1 Additional Day of Antibiotic Use	95% CI	P-value
#1	x.xx	(x.xx, x.xx)	x.xxx
#2	x.xx	(x.xx, x.xx)	x.xxx

[1] Analysis at Outcome Assessment Visit #1 uses the subset of the CC-V1 analysis population that did not receive systemic antibiotic unrelated to pneumonia on or prior to Day 5. Analysis at Outcome Assessment Visit #2 uses the subset of the CC-V2 analysis population that did not receive systemic antibiotic unrelated to pneumonia on or prior to Day 18.

[2] Odds ratio of an OCR at Outcome Assessment Visit #1 greater than k for the effect of one additional day of use of antibiotic, where k is any observed OCR value (1, 2, 3, …) besides the highest observed value.

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.1.1 Solicited Adverse Events

Table 49: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Treatment Group

Symptom	Day 1 Standard Course (N=X)			Day 1 Short Course (N=X)			Day 2 Standard Course (N=X)			Day 2 Short Course (N=X)			Day 3 Standard Course (N=X)			Day 3 Short Course (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Irritability																		
Vomiting																		
Diarrhea																		
Allergic Reaction																		
Stomatitis																		
Candidiasis																		

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.
[Table will be continued for Day 4, Day 5, Days 6-9 combined, Days 10-13 combined, Days 12-14-18 combined, Days 19-25 combined, and all days combined.]

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Standard Course

Symptom	Severity	Standard Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Irritability	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Vomiting	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Diarrhea	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Allergic Reaction	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Stomatitis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Candidiasis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Standard Course *(continued)*

Symptom	Severity	Standard Course								
		Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Short Course

Symptom	Severity	Short Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Irritability	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Vomiting	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Diarrhea	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Allergic Reaction	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Stomatitis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Candidiasis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Short Course *(continued)*

Symptom	Severity	Short Course								
		Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table 52: Number and Percentage of Subjects Experiencing Solicited Adverse Events or Cough of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group

Symptom	Severity	Standard Course (N=X)		Short Course (N=X)		Odds Ratio (95% CI)	P-Value
		n (%)	95% CI	n (%)	95% CI		
Any Symptom	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Irritability	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Stomatitis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 53: Listing of Serious Adverse Events

Part 1

Subject ID	Treatment Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	# of Days Post Dose the Event Became Serious	Duration (Days)	Reason Reported as an SAE	Severity

Part 2

Subject ID	Adverse Event	Relationship to Study Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Laboratory Data Over Time

Not applicable

14.3.5 Displays of Laboratory Results

Not applicable

14.3.6 Displays of Vital Signs

Table 54: Summary of Vital Signs by Visit and Treatment Group

		Enrollment Visit		Outcome Assessment Visit #1		Outcome Assessment Visit #2	
		Standard Course	Control	Standard Course	Control	Standard Course	Control
Temperature (°F)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Respiratory Rate (breaths/min.)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Pulse (beats/min.)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx

14.4 Summary of Concomitant Medications

Table 55: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

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

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

Table 56: Medically Attended Visits

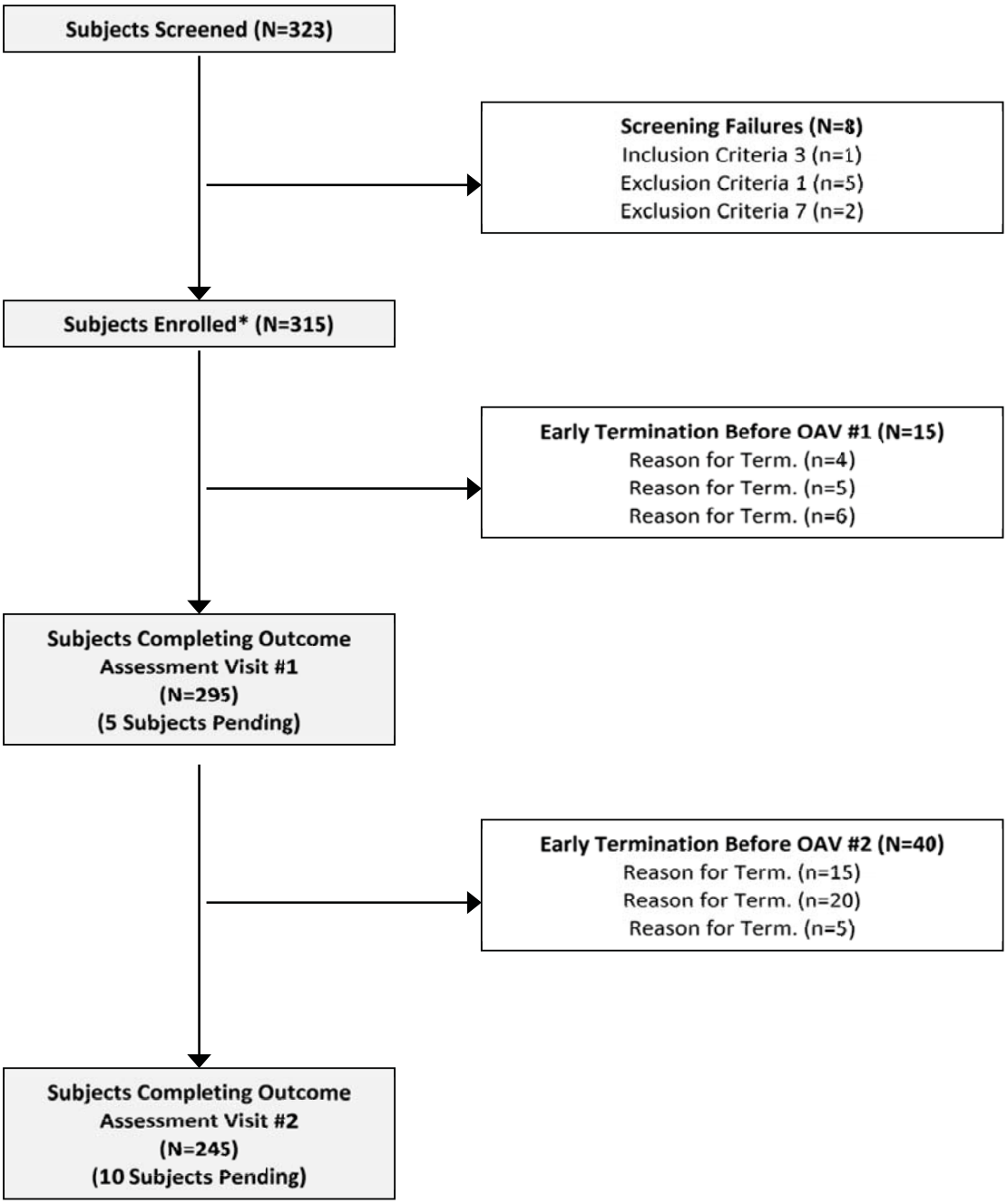
	Day 1-5		Day 6-18	
	Standard Course n (%) (N=X)	**Short Course n (%) (N=X)**	**Standard Course n (%) (N=X)**	**Short Course n (%) (N=X)**
Emergency Department Visit[1]				
Primary Care Provider Visit[1]				
Study Physician Visit[1]				
Urgent Care Visit[1]				
Other Medically Attended Visit[1]				
Additional Antibiotic Received[2]				
Drainage of pleural fluid[2]				
Placement of a chest tube[2]				
Video assisted thoracoscopic surgery[2]				
Thoracotomy procedure[2]				
Any other surgical procedure[2]				
Hospitalization[2]				

1 Visit associated with worsening study pneumonia.
2 For pneumonia or a complication of pneumonia.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

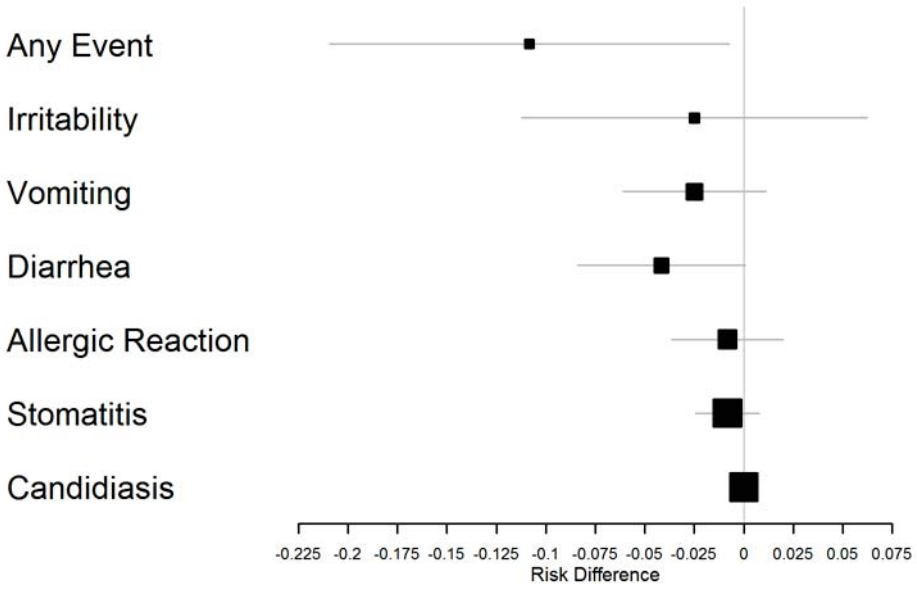
Figure 2: CONSORT Flow Diagram



*All enrolled subjects will be evaluable for the primary (ITT) analysis.

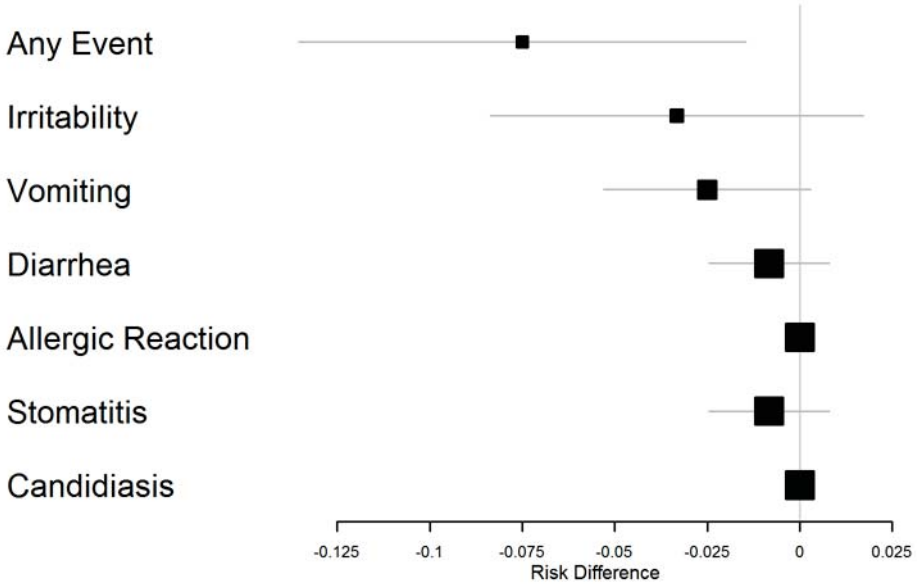
[Programming Note: Diagram will include breakdown by treatment arm.]

Figure 3: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Mild, Moderate, or Severe - CC-V1 Population



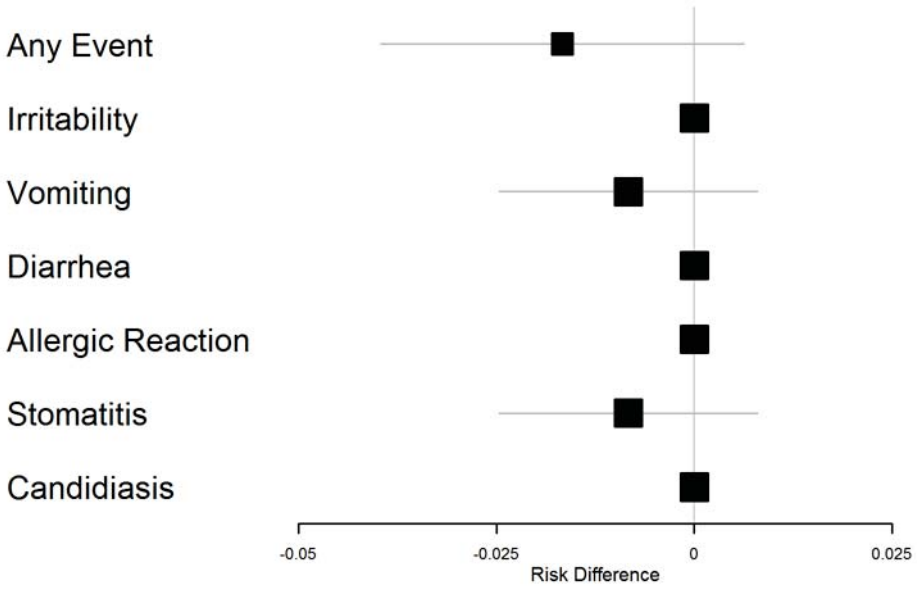
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 4: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Moderate, or Severe - CC-V1 Population



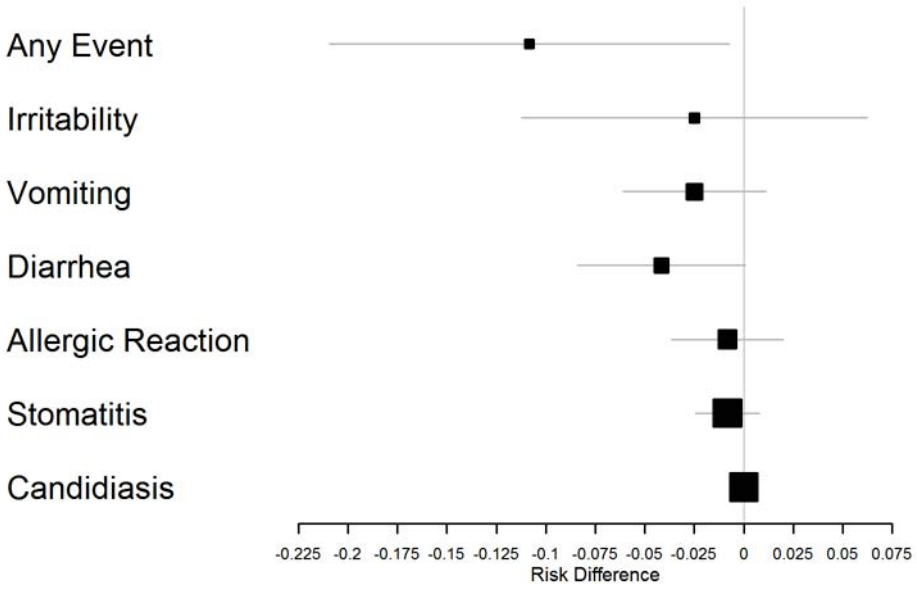
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 5: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Severe - CC-V1 Population



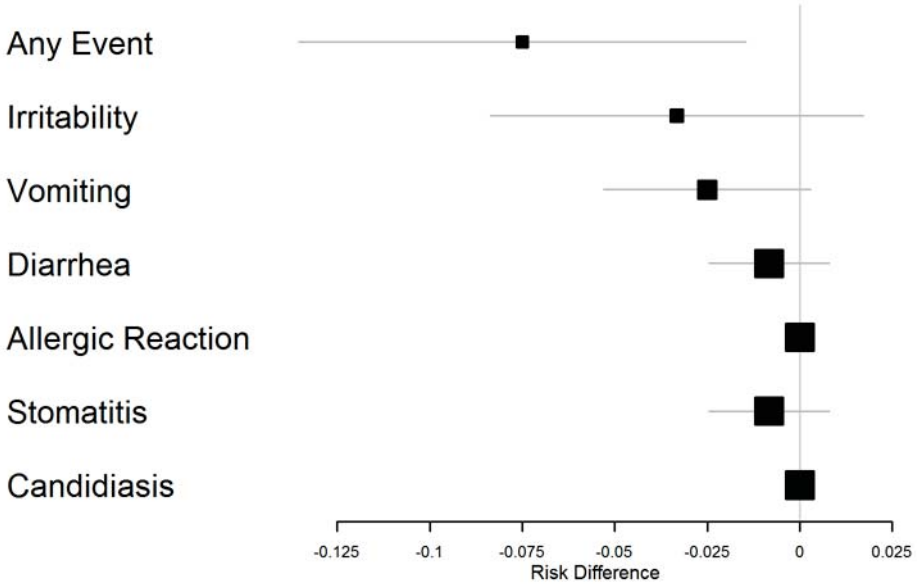
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 6: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Mild, Moderate, or Severe - CC-V2 Population



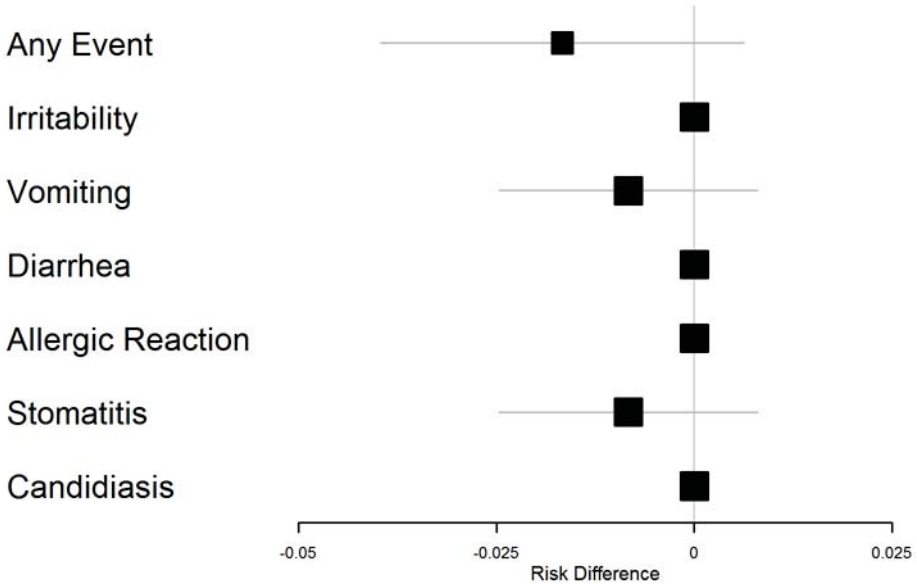
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 7: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Moderate, or Severe - CC-V2 Population



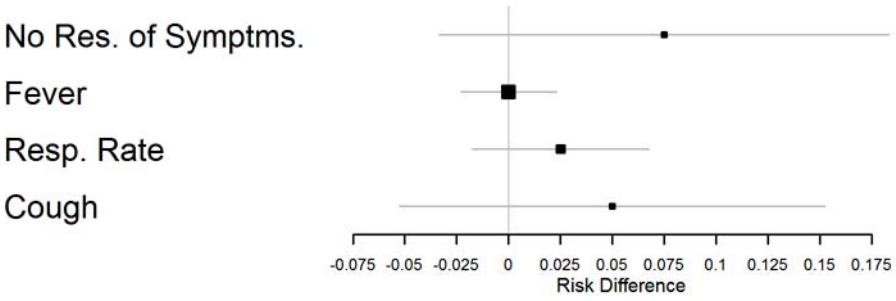
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 8: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Severe - CC-V2 Population



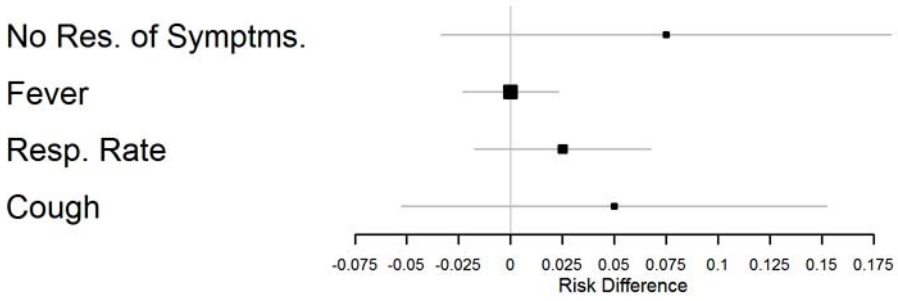
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 9: Forest Plot of Risk Difference of Lack of Resolution of Symptoms and Its Components - Outcome Assessment Visit #1 - CC-V1 Population



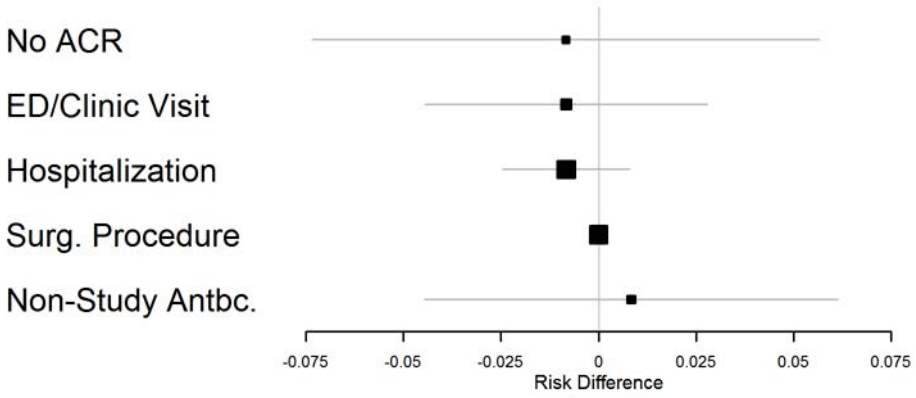
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 10: Forest Plot of Risk Difference of Lack of Resolution of Symptoms and Its Components - Outcome Assessment Visit #2 - CC-V2 Population



Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 11: Forest Plot of Risk Difference of Lack of Adequate Clinical Response and Its Components - Outcome Assessment Visit #1 - CC-V1 Population

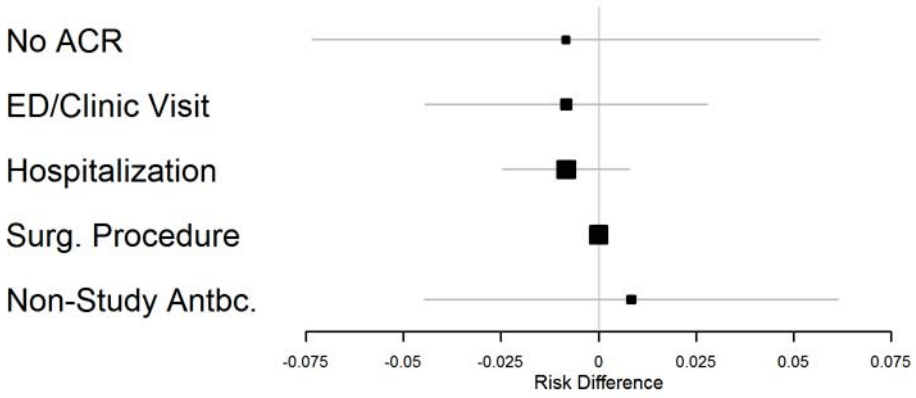


Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 12: Forest Plot of Risk Difference of Any Receipt of Non-Study Antibiotics or Medically Attended Visit - Outcome Assessment Visit #1 - CC-V1 Population

[Figure 12 will repeat Figure 11 without the No ACR confidence interval and will show confidence intervals for all events Day 1 – Day 5 (ED/Clinic Visit, Hospitalization, Surgical Procedure, and receipt of Non-Study Antibiotic) rather than only those satisfying the definition for lack of adequate clinical response.]

Figure 13: Forest Plot of Risk Difference of Lack of Adequate Clinical Response and Its Components - Outcome Assessment Visit #2 - CC-V2 Population

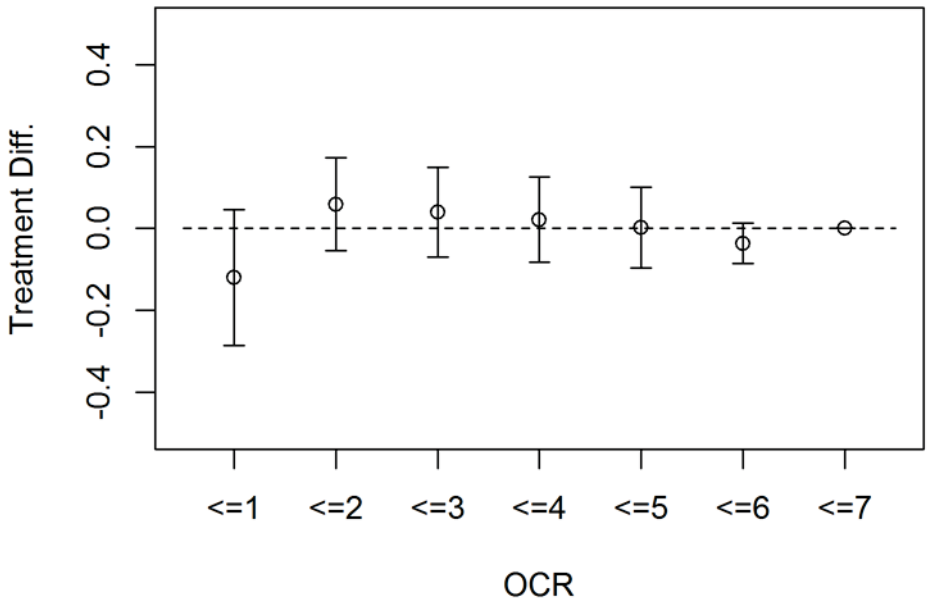


Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 14: Forest Plot of Risk Difference of Any Receipt of Non-Study Antibiotics or Medically Attended Visit - Outcome Assessment Visit #2 - CC-V2 Population

[Figure 14 will repeat Figure 13 without the No ACR confidence interval and will show confidence intervals for all events Day 1 – Day 18 (ED/Clinic Visit, Hospitalization, Surgical Procedure, and receipt of Non-Study Antibiotic) rather than only those satisfying the definition for lack of adequate clinical response.]

Figure 15: 95% Cumulative Difference Plot[1] of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - ITT Analysis



[1] Plots the 95% confidence intervals of the difference in the probability Pr(OCR≤k | treatment=m), where k=1,2,3,4,5,6,7 and m=0,1, between the two treatment groups. Note there can be no difference in Pr(OCR≤8 | treatment=m) since the probability is always 1 for each treatment arm, so only the first seven levels of the OCR are plotted.

Figures with similar format:

Figure 16: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - CC-V1 Analysis

Figure 17: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - ATP-V1 Analysis

Figure 18: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - Worst Case Analysis

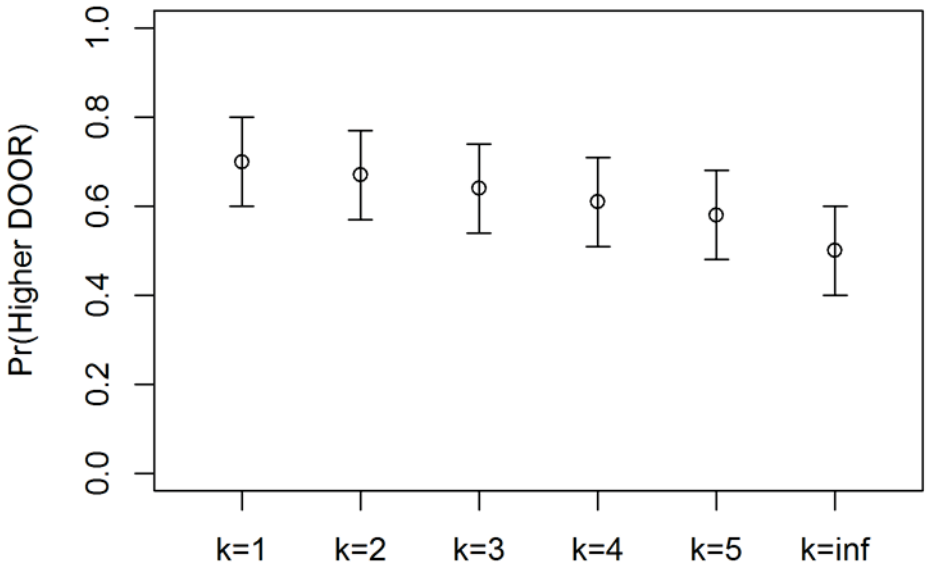
Figure 19: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - ITT Analysis

Figure 20: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - CC-V2 Analysis

Figure 21: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - ATP-V2 Analysis

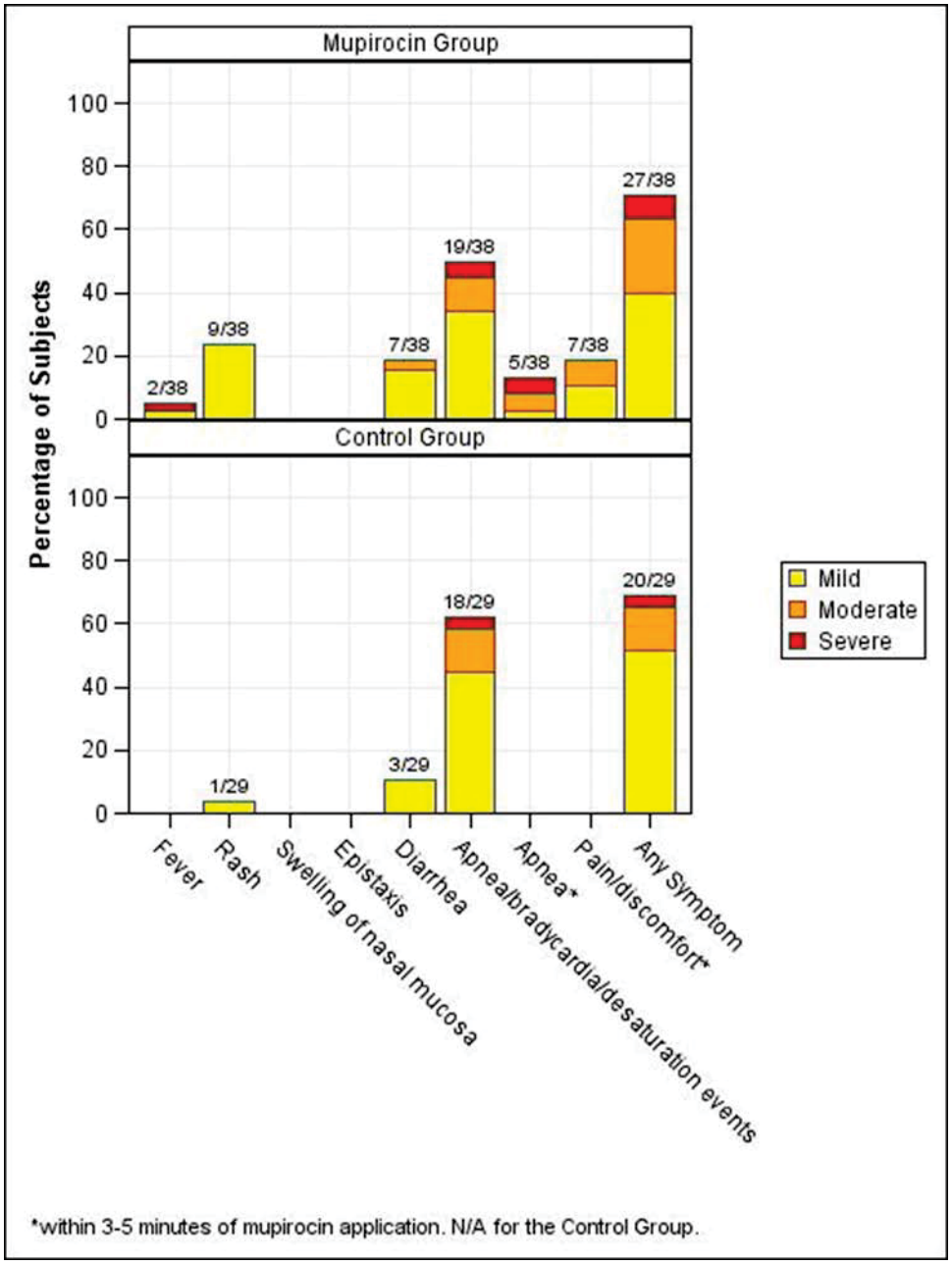
Figure 22: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - Worst Case Analysis

Figure 23: C-V1 Evaluation of DOOR at Outcome Assessment Visit #1 - Minimum Required Difference in Days for Antibiotic Use "Tie-Breaking" Varies k=1,2,3,4,5, or Infinity



14.3.1.1 Solicited Adverse Events

Figure 24: Maximum Severity of Solicited Adverse Events (by Symptom)



[Programming Note: This figure will present maximum severity of solicited events separately by treatment group. The mockup is an example only. The actual figure will contain treatment groups and solicited events relevant to the 14-0079 protocol.]

14.3.5 Displays of Laboratory Results

Not applicable

APPENDIX 3. LISTINGS MOCK-UPS

LIST OF LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

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

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 - Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1 - Subject-Specific Protocol Deviations

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

Listing 3: 16.2.2.2 - Non-Subject-Specific Protocol Deviations

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3 - Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., CC-V1, ATP-1]	[e.g., CC-V2, ATP-2]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis. No subjects are excluded from ITT analyses.

16.2.4 Demographic Data

Listing 5: 16.2.4.1 - Demographic Data

Treatment Group	Subject ID	Sex	Initial Antibiotic	Initial Site of Treatment	Age at Enrollment (months)	Ethnicity	Race

[Implementation Note: If a subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."]

Listing 6: 16.2.4.2 - Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

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

Listing 7: 16.2.5 - Treatment Compliance

Treatment Group	Subject ID	Dose(s) Missed	Extra Doses
		[1,2,3,4,5,6,7,8,9,10]	

16.2.6 Solicited Events

Listing 8: 16.2.6 - Solicited Events

Treatment Group	Subject ID	Study Day	Irritability	Vomiting	Diarrhea	Allergic Reaction	Stomatitis	Candidiasis

16.2.7 Serious Adverse Events

Listing 9: 16.2.7 - Serious Adverse Events

Subject ID	Treatment Group	AE Number	Adverse Event	SAE Onset Date	Study Day	Duration (days)	Reason Reported as an SAE	Severity	Relationship to Study Product

Subject ID	Relationship to Study Product	Alternate Etiology, if not related	Outcome	Action Taken with Study Treatment	Subject Discontinued Due to SAE	MedDRA® System Organ Class	MedDRA® Preferred Term	Comments

16.2.8 Vital Signs and Physical Exam Findings

Listing 10: 16.2.8.1 - Vital Signs

Treatment Group	Subject ID	Visit Number	Temperature (°F)	Respiration Rate (breaths/min)	Pulse (beats/min)

Listing 11: 16.2.8.2 - Physical Assessment Findings

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.9 Concomitant Medications

Listing 12: 16.2.9 - Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

16.2.10 Medically Attended Visits

Listing 13: 16.2.10.1 - Medically Attended Visits - Standard Course

Subject ID	Visit Study Day	Visit Type[1]	Antibiotic[1]	Surgery[1]	Hospitalization[1]	Hospital Admit Day	Hospital Discharge Day

[1]Asterisk indicates the visit, antibiotic, surgery, or hospitalization were due to pneumonia or a complication of pneumonia.

Listing 14: 16.2.10.2 - Medically Attended Visits - Short Course

Subject ID	Visit Study Day	Visit Type[1]	Antibiotic[1]	Surgery[1]	Hospitalization[1]	Hospital Admit Day	Hospital Discharge Day

[1]Asterisk indicates the visit, antibiotic, surgery, or hospitalization were due to pneumonia or a complication of pneumonia.

16.2.11 Cough

Listing 15: 16.2.11.1 - Cough - Standard Course

	Cough Severity by Study Day or Visit																										
Subject ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**OAV[1]#1**	**OAV[1]#2**	**ETV[2]**

[1] OAV = Outcome Assessment Visit
[2] ETV = Early Termination Visit

Listing 16: 16.2.11.2 - Cough - Short Course

	Cough Severity by Study Day or Visit																											
Subject ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**OAV[1]#1**	**OAV[1]#2**	**ETV[2]**

[1] OAV = Outcome Assessment Visit
[2] ETV = Early Termination Visit

16.2.12 Presence of Fever in Previous 24 Hours

Listing 17: 16.2.12.1 - Presence of Fever in Previous 24 Hours - Standard Course

Subject ID	Outcome Assessment Visit #1		Outcome Assessment Visit #2		Early Termination Visit	
	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]

[1] Recorded oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F)
[2] Fever attributed to a process unrelated to the prior diagnosis of pneumonia

[Programming Note: Listing programmed from ACRTEMP and ACRFEV only.]

Listing 18: 16.2.12.2 - Presence of Fever in Previous 24 Hours - Short Course

Subject ID	Outcome Assessment Visit #1		Outcome Assessment Visit #2		Early Termination Visit	
	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]

[1] Recorded oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F)
[2] Fever attributed to a process unrelated to the prior diagnosis of pneumonia

16.2.13 Ordinal Clinical Response and DOOR, According to CC-V1 and CC-V2 Analyses[1]

Listing 19: 16.2.13 - Ordinal Clinical Response and DOOR, According to CC-V1 and CC-V2 Analyses[1]

Subject ID	Treatment Group	Outcome Assessment Visit #1			Outcome Assessment Visit #2		
		Ordinal Clinical Response	Days of Antibiotic Use	DOOR	Ordinal Clinical Response	Days of Antibiotic Use	DOOR

[1] Ordinal Clinical Response, Days of Antibiotic Use, and DOOR at Outcome Assessment Visits #1 and #2 are only listed for subjects that had the respective Outcome Assessment Visit (no imputed values are shown).

APPENDIX 4. NCA TEMPLATE

See separate document, if applicable.

CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 14-0079
Study Title:
A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)

NCT02891915

Version 2.0

DATE: 24FEB2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 14-0079**
Development Phase:	Phase IV
Products:	Amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos
Form/Route:	Oral suspensions
Indication Studied:	Community Acquired Pneumonia
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	04OCT2016
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	24FEB2020
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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TABLE OF CONTENTS *(continued)*

TABLE OF CONTENTS *(continued)*

LIST OF ABBREVIATIONS

ACR	Adequate Clinical Response
AE	Adverse Event/Adverse Experience
ATC	Anatomical Therapeutic Classification
ATP	According-to-Protocol
CAP	Community Acquired Pneumonia
C	Celsius
CAR	Clinical Agents Repository
CC	Complete Case
CC-V1	Complete Case at Outcome Assessment Visit #1 Analysis Population
CC-V1	Complete Case at Outcome Assessment Visit #2 Analysis Population
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOOR	Desirability of Outcome Ranking
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EHR	Electronic Health Record
F	Fahrenheit
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
h	Hours
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDES	Internet Data Entry System

LIST OF ABBREVIATIONS *(continued)*

IDSA	Infectious Diseases Society of America
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-to-Treat
kg	Kilogram
L	Liter
MAR	Missing at Random
MAV	Medically Attended Visit
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
N	Number (typically refers to subjects)
NIH	National Institutes of Health, DHHS
OAV	Outcome Assessment Visit
OCR	Ordinal Clinical Response
OHRP	Office for Human Research Protections
PI	Principal Investigator
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
RADAR	Response Adjusted for Days of Antibiotic Risk
RR	Respiratory Rate
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SCOUT	Short Course Therapy for Urinary Tract Infections in Children

LIST OF ABBREVIATIONS *(continued)*

SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
Std	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
USP	United States Pharmacopeia

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)" (DMID protocol 14-0079) describes and expands upon the statistical information presented in the protocol.

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

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

2. INTRODUCTION

This is a Phase IV, blinded, placebo-controlled, multi-center, randomized trial with a primary objective to compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with community acquired pneumonia (CAP) assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy. Subjects are randomized 1:1 to either an additional 5 day course of their initially prescribed antibiotic (10 days total antibiotic therapy), or 5 days of a matching placebo (5 days total antibiotic therapy). Randomization is stratified by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility). Randomization is not stratified by clinical site.

The study follows a variety of clinical outcomes including 1) persistence of fever, tachypnea, or cough; 2) medically attended visits for persistent or worsening pneumonia; and 3) solicited events.

2.1. Purpose of the Analyses

A composite of the clinical outcomes and number of days of antibiotic use is used to define the DOOR and assess the overall superiority of short course treatment. Superiority of DOOR using clinical outcomes from the first 5 study days and at Outcome Assessment Visit #1 will be the primary analysis. Superiority of DOOR using clinical outcomes from the first 18 days and at Outcome Assessment Visit #2 will be a secondary analysis. For both analyses, all components of the DOOR will also be analyzed individually.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

1. To compare the composite overall outcome (Desirability of Outcome Ranking, DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #1 (Study Day 8 +/- 2 days).

3.1.2. Secondary Objectives

1. To compare the composite overall outcome (DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visit #2 (Study Day 22 +/- 3 days).
2. To compare the resolution of symptoms (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.
4. To compare solicited events (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.
5. To compare medically attended visits to Emergency Departments (ED) or outpatient clinics, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics (components of the clinical response) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2.

3.1.3. Exploratory Objectives

1. To examine the robustness of results of DOOR comparisons when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a 1 day difference to a 2, 3, 4, or 5 day difference.

3.2. Endpoints

3.2.1. Primary Endpoints

The primary endpoint/outcome measure is the DOOR at Outcome Assessment Visit #1.

3.2.2. Secondary Endpoints

Secondary outcome measures include:

1. DOOR at Outcome Assessment Visit #2
2. Resolution of symptoms (a component of DOOR) at each outcome assessment visit, defined as the absence of fever, tachypnea, or cough of grade 2 or higher.
3. Adequate clinical response rates (a component of DOOR) at each outcome assessment visit, defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
4. Frequency of solicited events at each outcome assessment visit, as listed in Table 3.
5. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for persistent or worsening pneumonia (as defined below) at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations, surgical procedures, and receipt of non-study systemic antibiotics) will be compared between treatment groups.
6. Medically attended visits to ED or clinic; hospitalizations; surgical procedures; and receipt of non-study systemic antibiotics for all causes at each outcome assessment visit
    i. Individual event types (e.g., medical visits, hospitalizations surgical procedures, and receipt of non-study systemic antibiotic) will be compared between treatment groups.

3.2.3. Exploratory Endpoints

1. DOOR at Outcome Assessment Visits #1 and #2, when increasing the threshold in assigning different ranks due to differing numbers of days of antibiotic use from a 1 day difference to a 2, 3, 4, or 5 day difference.

3.3. Study Definitions and Derived Variables

DOOR is defined as follows:

1. Each subject is evaluated according to the ordinal composite outcome (See Table 1) and assigned an outcome rank ranging from 1-8. The ordinal outcome is referred to elsewhere in the SAP as the ordinal clinical response (OCR).
2. Desirability of Outcome Ranking (DOOR) is then assigned according to two rules:
    i. When comparing two subjects with different ordinal responses, the subject with a better ordinal response receives a higher rank.
    ii. When comparing two subjects with identical ordinal responses, the subject with fewer days of antibiotic use receives a higher rank.

The ordinal composite outcome involves an assessment of whether the subject has an adequate clinical response and whether they have experienced any solicited events as defined in Table 1.

Table 1: Ordinal Outcome

	Adequate clinical response[1] (Assessed at Outcome Assessment Visits #1 and #2)	Solicited events[3] (Assessed at Outcome Assessment Visits #1 and #2)
1	Yes, with resolution of symptoms[2]	None
2	Yes, with resolution of symptoms[2]	Mild (Grade 1)
3	Yes, with resolution of symptoms[2]	Moderate (Grade 2)
4	Yes, with resolution of symptoms[2]	Severe (Grade 3)
5	Yes, with persistent symptoms of fever, tachypnea, or cough	None or any grade
6	No, with ED/clinic visit but no hospitalization	None or any grade
7	No, with hospitalization	None or any grade
8	Death from any cause	

[1] Adequate clinical response is defined as the absence of a medically attended visit to an ED or outpatient clinic or hospitalization for persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
• Persistent or worsening pneumonia is defined as receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
• Note: Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.
[2] Resolution of symptoms is defined as the absence of all of the following:
• Oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding the Outcome Assessment Visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia;
• Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit;
• Presence of cough grade 2 or 3 at the Outcome Assessment Visit, defined as Grade 0 (no cough), Grade 1 (Occasional coughing [less than 4 times hourly]), Grade 2 (frequent coughing [4 or more times an hour], interferes with sleep), Grade 3 (almost constant coughing (never free of cough), makes sleep nearly impossible);
[3] Solicited events will be captured daily until Outcome Assessment Visit #2; thereafter, parents/legal guardians will report symptoms based on memory aid and medical interview by study staff. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Day 1: Day 1 begins at the time the first dose of study product is administered and ends at 11:59 PM of that same day. If a subject has no recorded receipt of study product at the time of the analysis, then Day 1 will be defined as the date 5 days after the date of initiation of the initial antibiotic.

DOOR at Outcome Assessment Visit #1: Defined as above, using DOOR components from the following Study Days.

Adequate Clinical Response: Day 1 – Day 5

Resolution of Symptoms:

- Fever as measured in the 24 hours prior to Outcome Assessment Visit #1. If a subject has a fever according to a single measurement, but no repeat measurement after at least 15 minutes has been performed, the subject will be analyzed as having a fever. If a subject has a fever according to the measurement taken as a part of vital signs

during Outcome Assessment Visit #1, the subject will be analyzed as having a fever at Outcome Assessment Visit #1. If the vital signs measurement shows no fever, and the parental assessment of fever during the previous 24 hours is missing, then fever will be treated as missing.

- Respiratory Rate and Cough: determined at Outcome Assessment Visit #1

Solicited Events: Day 1 – Day 5

Number of Days of Antibiotic Use: Day 1 – Day 5

DOOR at Outcome Assessment Visit #2: Defined as above, using DOOR components from the following Study Days.

Adequate Clinical Response: Day 1 – Day 18

Resolution of Symptoms:

- Fever as measured in the 24 hours prior to Outcome Assessment Visit #2. If a subject has a fever according to a single measurement, but no repeat measurement after at least 15 minutes has been performed, the subject will be analyzed as having a fever. If a subject has a fever according to the measurement taken as a part of vital signs during Outcome Assessment Visit #2, the subject will be analyzed as having a fever at Outcome Assessment Visit #2. If the vital signs measurement shows no fever, and the parental assessment of fever during the previous 24 hours is missing, then fever will be treated as missing.
- Respiratory Rate and Cough: determined at Outcome Assessment Visit #2

Solicited Events: Day 1 – Day 18

Number of Days of Antibiotic Use: Day 1 – Day 18

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a multi-center, randomized, double-blind, placebo-controlled, superiority clinical trial evaluating short course (5 day) vs. standard course (10 day) of oral beta-lactam antibiotic therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) for treatment of CAP in children 6-71 months of age who have clinically improved prior to enrollment. The study will randomize approximately 400 enrolled subjects to one of the two study arms (approximately 200 children in each arm) in order to reach 360 evaluable subjects. Subjects will be randomized (1:1) to receive either a standard course of the initially prescribed antibiotic (10 days) or a short course of the initially prescribed antibiotic (5 days) plus 5 days of matching placebo.

The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Day -5 is defined as the date on which oral beta-lactam therapy is initiated for a diagnosis of CAP. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. These subjects will be assessed for eligibility and enrolled on Day -3 to -1 of their initially prescribed oral beta-lactam therapy. Subjects may also be enrolled on Day 1 (the first day of receipt of study agent) provided they have not yet received any doses of the healthcare provider-prescribed antibiotic therapy for that day.

Visit 1: Enrollment Visit. Subjects who meet the eligibility criteria, and whose parent/guardian consents for participation in the study, will complete an Enrollment Visit on Day -3 to -1. Subjects satisfying the inclusion criteria with no exclusion criteria will be enrolled and randomized. Enrolled subjects will continue to receive the initially prescribed antibiotic through Day -1. The subjects' parents/guardians will be instructed to contact study personnel if their child develops fever or worsening respiratory symptoms (worsening cough, increased work of breathing, any other concerning symptoms in the parents' estimation) following enrollment.

Randomization: Enrolled subjects will be randomized to short vs. standard course therapy at a 1:1 ratio, with stratification by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility).

Intervention: Subjects will continue on the initially prescribed antibiotic through Day -1, until they have completed 5 days (i.e., 5 scheduled doses of once daily medication, 10 scheduled doses of twice daily medication) of antibiotic therapy [e.g., if a subject takes the first dose of antibiotic in the afternoon of Day -5, the first dose of study agent would occur on the afternoon of Day 1, providing 10 total scheduled doses of a twice daily prescribed antimicrobial]. The first day of receipt of study agent will be Day 1. Subjects assigned to standard course therapy will receive 5 additional days (10 doses) of the same initially prescribed antibiotic, with standardized twice-daily dosing. Subjects assigned to short course therapy will receive 5 more days (10 doses) of a matching placebo. Both the study agent and placebo may appear different than the commercial formulation the child originally received. The placebo will appear indistinguishable in color, taste, thickness, and consistency from the active antibiotic the child would otherwise

receive in the study. The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation.

Follow-up and Assessment of Endpoints: Subjects will be scheduled for the following assessment visits:

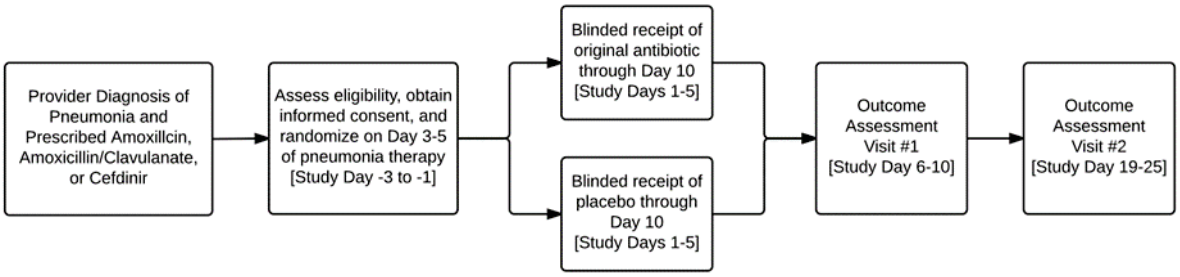
Visit 2: Outcome Assessment Visit #1, Day 6 to 10 (1-5 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Visit 3: Outcome Assessment Visit #2, Day 19 to 25 (14-20 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence of any solicited events; and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects who are identified as having an inadequate clinical response prior to Outcome Assessment Visit #1 will be asked to complete Outcome Assessment Visits #1 and #2, in order to evaluate the occurrence of any solicited events and the duration of antibiotic therapy (both study product/placebo and any additional oral or parenteral antibiotic therapy prescribed by study or non-study providers).

Subjects will be invited to contribute oropharyngeal and stool specimens at specified times throughout the study for future use. Additional informed consent will be obtained for future use sample collection.

Figure 1: Schematic of the Study Design



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

In 2014, a randomized trial of short vs. standard course therapy in young children in Israel with CAP suspected to be of bacterial origin found a higher rate of treatment failure (40%) in subjects treated for only 3 days vs. subjects treated for 5 or 10 days (Greenberg 2014). The study was underpowered to detect a difference in treatment failure between subjects treated for 5 vs. 10 days, but treatment failure did not occur in either group.

The proposed study will test the effectiveness of short (5-day) vs. standard (10-day) course therapy in children who are diagnosed with CAP and initially treated in outpatient clinics, urgent

care facilities, and emergency departments. The study will specifically address whether short course therapy is superior to standard therapy among children that have clinically improved since diagnosis. If superior to standard course therapy, short course therapy could reduce antibiotic exposure among young children. We will use a study methodology similar to the SCOUT Study ("Short Course Therapy for Urinary Tract Infections in Children")—a randomized, double-blind, placebo-controlled non-inferiority trial of short course antimicrobial therapy for urinary tract infection in children sponsored by NIAID through the "Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance" initiative. However, the SCOUT-CAP trial will use a superiority study design using an ordinal composite overall outcome (Desirability of Outcome Ranking, DOOR, see Protocol Section 3.2.1 Primary Outcome Measures)—to test the hypothesis that short course (5 day) therapy is superior to standard course (10-day) beta-lactam therapy in children who have experienced early clinical improvement of pneumonia.

The potential risk of short course therapy is that clinical outcomes may not be equivalent to standard course therapy. Specifically, the percent of children with adequate clinical response (or in this case, no relapse of illness) may be lower in children receiving short course therapy. Adequate clinical response can be defined as resolution or substantial improvement in clinical signs and symptoms (e.g., fever, cough, respiratory rate, work of breathing) and the lack of need for additional antibiotic therapy, additional contacts with the health care system, or surgical procedures for worsening pneumonia. The magnitude of this risk is not well established, although a study from Israel suggests it is small (Greenberg 2014); nevertheless, this degree of risk will be evaluated during this trial.

4.3. Selection of Study Population

Subjects who are diagnosed with CAP in emergency departments (EDs), urgent care facilities, and clinics will be screened for eligibility. Screening will continue until 400 subjects are enrolled cumulatively across all the study sites. The study will recruit potential subjects from children who are diagnosed with CAP and who are initiated on antibiotic therapy using oral beta-lactam therapy (amoxicillin, amoxicillin-clavulanate, cefdinir) by healthcare providers in EDs, outpatient clinics, and urgent care centers at the study sites. Potential subjects will be identified at any time following clinical diagnosis of pneumonia. Other forms and/or mechanisms of recruitment may also be used. The local IRB will approve recruitment materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

4.3.1. Inclusion Criteria

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

4.3.2. Exclusion Criteria

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

4.3.3. Reasons for Withdrawal

Subject Withdrawal

Subjects' parents/guardians 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
- Any new information becomes available that makes further participation unsafe.

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

Discontinuation of Treatment

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

4.4. Treatments

4.4.1. Treatments Administered

All active and placebo study products will be orally administered via oral dosing syringe or dosing cup. For older children in whom a dosing cup is preferred, parents will be instructed to measure the drug in the oral dosing syringe prior to transferring to the dosing cup.

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

Per International Conference 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. Subjects will be assigned to either placebo or active study drug (the same antibiotic that they were prescribed for the first 5 days of treatment). After a subject is enrolled, they will be given a random treatment assignment of study product to either short course or standard course therapy. Randomization to short vs. standard course therapy will be at a 1:1 ratio (approximately 200 subjects per treatment group). Subjects will be stratified by age group <24 months vs. 24-71 months), type of initial antimicrobial therapy, and initial treatment in an ED or outpatient clinic/urgent care center.

Enrollment of subjects will be performed online using the electronic data capture (EDC) system provided by the Statistical and Data Coordinating Center (SDCC). The list of randomized treatment assignments will be prepared by statisticians at the SDCC. The list will be used to assign each volunteer a treatment code after the necessary data have been entered into the EDC

system. A designated individual 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.

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

4.4.3. Blinding

This is a double-blind clinical trial. The study subjects and their parents/guardians, investigators, and study team staff will remain blinded to study treatment assignment throughout the study. The subjects and their families, investigators, and study team staff will not be blinded to which of the three antibiotics (amoxicillin, amoxicillin-clavulanate, cefdinir) the subject was initially prescribed.

The study products and placebo will be prepared by the unblinded site Research Pharmacist. Only the pharmacy staff will be aware of the study product bottle assignments. For subjects randomized to standard course therapy, the pharmacy will provide the same medication prescribed initially. For subjects randomized to short course therapy, the pharmacy will provide a placebo that resembles the appearance (color and texture), flavor, and consistency of the active study product. All study products will be packaged with an identical appearance. Additional details regarding dispensing procedures will be included in the protocol-specific MOP.

The study product will be labeled with a numerical code that masks site investigators, site staff, parent(s)/guardian(s) and children to the formulation. The unblinded site Research Pharmacist will be the only person to perform the unmasking if needed. Additional details regarding labeling procedures will be included in the protocol-specific MOP.

During the consenting process it will be explained to the parents of any potential subjects that the study product (treatment or placebo) that will be provided for administration after Day 5, may or may not taste exactly the same as the originally prescribed medication, and that the look and smell may be slightly different because it might be supplied by a different manufacturer than that of the initially prescribed antibiotic. Parents will also be instructed that the amount or frequency of the prescribed study product has been made uniform across all study groups; therefore, the amount/frequency may be different than originally prescribed by their provider (e.g., receipt of once daily cefdinir is not excluded, but upon study entry, those subjects will receive either twice daily cefdinir or placebo).

4.5. Study Variables

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

As the safety profile of amoxicillin, amoxicillin-clavulanate, and cefdinir are well established, and this trial is not powered to detect new, unknown safety signals, there will be no unsolicited event collection during this study and only protocol-defined SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected.

For a complete list of SAEs that will be collected, regardless of the relationship to the study drug, see the Protocol. SAEs will be graded for severity and assessed for relationship to study product.

See the Protocol for the schedule of events for this study.

Severity of Event: SAEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Relationship to Study Product: The study physician's assessment of an SAE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in this study. If there is any doubt as to whether a clinical observation is an SAE, the event should be reported. The relationship to study product must be assessed for SAEs using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

All SAEs will be:

- Assessed for severity and causal relationship by a physician listed on the Form FDA 1572 as the principal investigator (PI) or sub-investigator.
- Recorded on the appropriate SAE report form.
- Followed through resolution by a study physician.
- Reviewed by the safety monitor, the DSMB (periodic review unless associated), DMID Medical Monitor, and the local IRB.

Death, life-threatening events, hospitalization or prolongation of existing hospitalization, and other important medical events are part of the efficacy endpoints of this trial and will not be reported or collected as SAEs, unless meeting the SAE reporting criteria included in the Protocol.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group.

In addition to the SAE form, selected SAE data fields must also be entered into the EDC web-based data entry system. Refer to the Manual of Procedures for details regarding this procedure. Timelines for submission of an SAE form are as follows:

- All non-accidental deaths and life-threatening events, regardless of relationship, will be recorded on the SAE form and sent by fax within 24 hours of site awareness of the death or event.
- All other SAEs, regardless of relationship, will be reported via fax by the site within 24 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the subject to be stable.

5. SAMPLE SIZE CONSIDERATIONS

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

H0: The sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 50% (i.e., no difference in DOOR).

The primary study sample size is based on a superiority test of the null hypothesis above, under an assumed alternative hypothesis that the sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR than if assigned to the 10-day arm plus one-half the probability of equal DOORs is 60% (p=60%).

A sample size of 360 (180 per arm) provides 90% power using a 2-sided alpha=0.05 with a Wilcoxon Mann-Whitney U test (see calculation below). If p=65% or 70%, then a total sample size of 160 (80 per arm) or 90 (45 per arm), respectively, would be required. The sample size is inflated by ~10% based on an estimate from a similar study, in order to account for loss to follow-up resulting in a total sample size of 400 (200/arm).

Sample size calculations were based on the formula below (Noether 1987):

$$N = \frac{\left(z_\alpha + z_\beta\right)^2}{12c(1-c)\left(p'' - \frac{1}{2}\right)^2}$$

$z_\alpha = \Phi^{-1}(0.975);\ z_\beta = \Phi^{-1}(0.90)$; (90% power for two-sided test with 5% Type I error)

$c = 0.5$ (equal allocation to treatment arms)

$p'' = 0.6$ (Pr(Higher DOOR) under alternative hypothesis)

Note that the primary analysis statistical methods use the ITT analysis population and will account for missing data with multiple imputation. The exact analysis method was not used for the power calculation because it would require an excessive amount of assumptions about the nature and patterns of missing data in the final dataset and relationships of components of the imputation model to the primary outcome. Instead, a complete case analysis assuming 90% evaluable for analysis was used to obtain approximately 90% power in the actual analysis.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

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

6.2. Timing of Analyses

One interim analysis will be performed and reported to the data and safety monitoring board (DSMB) after approximately 30% of the targeted subjects have completed the study. The interim analysis will inform DSMB decisions regarding stopping early for efficacy, futility, or safety.

The final analysis will be performed after database lock. Specific tables and figures may be released after DMID approval prior to CSR completion.

6.3. Analysis Populations

The primary analysis will be performed using the intention-to-treat (ITT) cohort. Other analyses, as specified below, may use complete case (CC) or according-to-protocol (ATP) cohorts. Analyses of the ITT cohort will include imputation for missing data, while analyses of CC and ATP cohorts will not contain missing data by design, because they are required to have sufficient data to define unambiguously the Outcome Assessment Visit #1 DOOR or Outcome Assessment Visit #2 DOOR.

Reasons for exclusion from each analysis population are summarized in Table 5 and shown by subject in Listing 4. Excluded subjects might satisfy multiple criteria justifying their exclusion, but will have only one reason indicated in Table 5 and Listing 4. The reason indicated will be determined by the following rules.

ITT Exclusions

- Subject became ineligible before taking study product.

CC-V1 Exclusions

- Subject not treated with study product
- Not excluded for any reason above, but early termination before Outcome Assessment Visit #1 (subjects will be tabulated by reason for termination)
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Adequate Clinical Response
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Resolution of Symptoms

- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Solicited Event Severity Days 1-5
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Number of Days of Antibiotic Use

CC-V2 Exclusions

- Subject not treated with study product
- Not excluded for any reason above, but early termination before Outcome Assessment Visit #2 (subjects will be tabulated by reason for termination)
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Adequate Clinical Response
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Resolution of Symptoms
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Solicited Event Severity Days 1-18
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #2 component: Number of Days of Antibiotic Use

ATP-V1 Exclusion Reasons

- The subject was excluded from CC-V1 cohort
- Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5
- Not excluded for any reason above, major protocol deviation (see Section 6.3.3; subjects will be tabulated by type of protocol deviation)
- Outcome Assessment Visit #1 occurred out of the protocol defined window of Day 6-10
- Outcome Assessment Visit #1 did not occur as an in-person visit

ATP-V2 Exclusion Reasons

- The subject was excluded from CC-V2 cohort
- Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5
- Not excluded for any reason above, major protocol deviation (see Section 6.3.3, subjects will be tabulated by type of protocol deviation)
- Outcome Assessment Visit #2 occurred out of the protocol defined window of Day 19-25
- Outcome Assessment Visit #2 did not occur as an in-person visit

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

The ITT cohort will include all randomized subjects that were still eligible on Day 1 of the study. The analyses on the ITT cohort will be performed per randomized treatment assignment.

Randomized subjects who became ineligible before Day 1 of the study and did not take any study product will be excluded from ITT. Subjects randomized but not treated for other reasons other than ineligibility will be analyzed in the ITT cohort, but will have adequate clinical response and its components treated as missing. Therefore, in ITT analyses, OCR and DOOR will be missing and will need to be imputed for subjects that were not treated. If data (solicited events, cough, etc.) are collected post-randomization for a subject that was not treated, that data will be used in the ITT analysis to assist in imputing the OCR and DOOR.

6.3.2. Complete Case (CC) Cohorts

Subjects in a CC analysis are analyzed as randomized but excluded from analysis if missing data prevents assigning an unambiguous value to the DOOR endpoint or if the subject has not received at least one dose of study product. The CC-V1 cohort will consist of all subjects with sufficient data to define unambiguously the Outcome Assessment Visit #1 DOOR. The CC-V2 cohort will consist of all subjects with sufficient data to define unambiguously the Outcome Assessment Visit #2 DOOR.

6.3.3. According-to-Protocol (ATP) Cohorts

Subjects in an ATP analysis require no major protocol deviations, and recorded receipt of at least one dose of study product each day from Day 1 to Day 5. What constitutes a major protocol deviation will be assessed on a case-by-case basis by a DMID/VTEU/ARLG committee prior to any member of the committee being unblinded to treatment assignments. Subjects in an ATP analysis will be analyzed as treated. The ATP-V1 cohort will restrict subjects to those in CC-V1 that furthermore meet the ATP requirements. The ATP-V2 cohort will restrict subjects to those in CC-V2 that furthermore meet the ATP requirements.

6.3.4. Safety Analysis Population

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

6.4. Covariates and Subgroups

Subjects will be recruited from multiple clinical sites, but randomization will not be stratified by site. Randomization will use a total of 12 strata, with stratification by 1) age group (<24 months vs. 24-71 months), 2) initially prescribed antibiotic (amoxicillin vs. amoxicillin-clavulanate vs. cefdinir), and 3) treatment site (emergency department vs. outpatient clinic/urgent care facility).

6.5. Missing Data

While all efforts will be made to minimize missing data, some missing data is expected. Whenever possible, subjects terminating from the study early will be given an early termination visit during which the available components of the DOOR and related measures can be recorded. The primary analysis will use multiple imputation with linear models to impute values using available information (treatment, randomization strata variables, and available visit information), assuming a missing at random (MAR) model. Secondary analyses will further examine the robustness of this analysis, including a “worst case analysis” in which all imputations of missing

data will be the worst case (result in the lowest possible DOOR given available information) for subjects in the 5-day arm and best case for subjects in the 10-day arm. Day 1 in this study is defined as the date of first receipt of study product. If a subject has no record of study product administration or did not receive a first dose of study product, but has other post-randomization data, Day 1 will be imputed as the date 5 days after the date of first receipt of initial antibiotic.

In some cases, a subject may have DOOR defined despite missing some of its components, in which case the subject will be eligible for inclusion into the CC and ATP analysis populations. In analyses of the components of the DOOR using the CC and ATP analysis populations, data will be analyzed as available and missing data will not be imputed.

The study includes several composite variables with rules for assignment, missingness, and imputation described below.

6.5.1. Adequate Clinical Response to OAV#1 or OAV#2

Subjects that have no record of receipt of at least one dose of study product will have adequate clinical response and its components considered missing at both OAV#1 and OAV#2. Otherwise, if a subject dies at any point during subject participation in the study, the subject will be considered as not having adequate clinical response at OAV#1 or OAV#2. Otherwise, if a subject does not have OAV#1 then ACR and its components are missing for OAV#1 and if a subject does not have OAV#2 then ACR and its components are missing for OAV#2.

Several variables are used to define the Adequate Clinical Response:

- MAVABRX: Was the subject prescribed or did the subject receive an additional antibiotic treatment at this visit? (Yes/No)
    - MAVABCP: If Yes, was the antibiotic given for pneumonia or treatment for a complication of pneumonia? (Yes/No)
- MAVPLEUR: Drainage of pleural fluid as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVCHTB: Placement of a chest tube as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVVIDEO: Video assisted thoracoscopic surgery as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVTHOR: Thoracotomy procedure as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVSURG: Any other surgical procedure as treatment for pneumonia or a complication of pneumonia? (Yes/No)
- MAVHOSP: Was the subject hospitalized at this visit? (Yes/No)
    - MAVHPPN: If Yes, was the hospitalization for the treatment of pneumonia or pneumonia complications? (Yes/No)

If a subject has OAV#1 and did not have a medically attended visit (MAV) from Day 1 to Day 5, inclusive, then the subject had adequate clinical response for OAV#1. If the subject had a MAV from Day 1 to Day 5 for which MAVABRX and MAVABCP were both YES (receipt of a non-

study systemic antibiotic for pneumonia), or for which MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were YES (treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures), then the subject did not have adequate clinical response at OAV#1. If the subject had a MAV from Day 1 to Day 5 for which MAVHOSP and MAVHPPN were both YES (subject was hospitalized for the treatment of pneumonia or pneumonia complications), then the subject did not have adequate clinical response at OAV#1. Otherwise, if the subject had a MAV from Day 1 to Day 5 and either MAVABRX was missing, MAVABRX was YES and MAVABCP was missing, or any of MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were missing, then adequate clinical response at OAV#1 is missing. Otherwise, if a subject has one or more MAVs from Day 1 to Day 5, with no MAV indicating receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures and no hospitalization for treatment of pneumonia or pneumonia complications and no MAV missing data as described, then the subject has adequate clinical response at OAV#1. Note that for determining whether the medical treatment or hospitalization falls within the period of Day 1 to Day 5, the date of the initial MAV will be used (MAVVISDT), rather than specific dates of surgery or hospitalization entered on the MAV form.

If a subject has OAV#2 and did not have a medically attended visit (MAV) from Day 1 to Day 18, inclusive, then the subject had adequate clinical response for OAV#2. If the subject had a MAV from Day 1 to Day 18 for which MAVABRX and MAVABCP were both YES (receipt of a non-study systemic antibiotic for pneumonia), or for which MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were YES (treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures), then the subject did not have adequate clinical response at OAV#2. If the subject had a MAV from Day 1 to Day 18 for which MAVHOSP and MAVHPPN were both YES (subject was hospitalized for the treatment of pneumonia or pneumonia complications), then the subject did not have adequate clinical response at OAV#2. Otherwise, if the subject had a MAV from Day 1 to Day 18 and either MAVABRX was missing, MAVABRX was YES and MAVABCP was missing, or any of MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were missing, then adequate clinical response at OAV#2 is missing. Otherwise, if a subject has one or more MAVs from Day 1 to Day 18, with no MAV indicating receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures and no hospitalization for treatment of pneumonia or pneumonia complications and no MAV missing data as described, then the subject has adequate clinical response at OAV#2. Note that for determining whether the medical treatment or hospitalization falls within the period of Day 1 to Day 18, the date of the initial MAV will be used (MAVVISDT), rather than specific dates of surgery or hospitalization entered on the MAV form.

The below pseudocode summarizes the logic for defining ACR at OAV#1.

```
if no recorded receipt of study product then ACR_OAV1=missing
else if death then ACR_OAV1=NO
```

```
else if subject does not have OAV#1 then ACR_OAV1=missing
else if subject has no MAV from Day 1 to Day 5 then ACR_OAV1=YES
else if subject has one or more MAVs from Day 1 to Day 5 with
      (MAVABRX=YES and MAVABCP=YES) or
      MAVPLEUR=YES or
      MAVCHTB=YES or
      MAVVIDEO=YES or
      MAVTHOR=YES or
      MAVSURG=YES or
      (MAVHOSP=YES and MAVHPPN=YES)
      then ACR_OAV1=NO
else if subject has MAV from Day 1 to Day 5 with
      MAVABRX=missing or
      (MAVABRX=YES and MAVABCP=missing) or
      MAVPLEUR= missing or
      MAVCHTB= missing or
      MAVVIDEO= missing or
      MAVTHOR= missing or
      MAVSURG= missing

then ACR_OAV1=missing
else ACR_OAV1=YES
```

6.5.2. Fever at OAV#1 or OAV#2

Two variables are used to define Fever at OAV#1 or OAV#2:

- ACRTEMP: Has the subject had a recorded temperature > 38.3 °C (100.9 °F) in the past 24 hours? (Yes/No)
- ACRFEV: If Yes, was fever attributed to a process unrelated to the prior diagnosis of pneumonia? (Yes/No)

Fever at Outcome Assessment Visit #1 and Fever at Outcome Assessment Visit #2 both involve several data components and have complex rules for when they are considered missing versus when fever is considered present or not present. The below logic describes the rules. Note that "fever is observed as a solicited event" only if a temperature of ≥ 38.3 °C (100.9 °F) was recorded on the day of the Outcome Assessment Visit or on the day prior to the Outcome Assessment Visit and either had no recorded confirmatory measurement at least 15 minutes after the first measurement or else the confirmatory measurement also indicated a temperature of ≥ 38.3 °C (100.9 °F). Fever at the OAV is never missing if the OAV did occur (specifically, ACRTEMP not missing), and the vital signs measurement at the visit and the actual temperatures reported by parents and recorded on the solicited events form (SRS) are treated as optional and supplemental data in the determination of the presence of fever at the visit.

- If the OAV did occur
    - If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is not indicated as unrelated to prior diagnoses of pneumonia (ACRFEV), then fever at the OAV is present

- If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is indicated as unrelated to prior diagnoses of pneumonia (ACRFEV), then fever at the OAV is absent
- If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is indicated as relatedness to prior diagnoses of pneumonia (ACRFEV) is missing, then fever at the OAV is missing
- If subject had a recorded temperature < 38.3 °C (100.9 °F) (ACRTEMP), then fever at the OAV is absent

6.5.3. Resolution of Symptoms at OAV#1 or OAV#2

Resolution of symptoms is defined as the absence of all of the following:

- Fever at the OAV, as defined above
- Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit (VS1.RESPB);
- Presence of cough grade 2 or 3 at the Outcome Assessment Visit (ACRCGHSV)

If the subject died at any point of participation in the study, then the subject will be analyzed as not having resolution of symptoms at either Outcome Assessment Visit. Otherwise, if the subject did not have adequate clinical response at OAV#1 or OAV#2, then the subject will be analyzed as not having resolution of symptoms at the respective Outcome Assessment Visit(s). Otherwise, if fever, elevated respiratory rate, or presence of grade 2 or 3 cough is indicated at OAV#1 or OAV#2, then the subject does not have resolution of symptoms at the respective Outcome Assessment Visit (regardless of whether some components of the resolution of symptoms are missing). Otherwise, if fever, respiratory rate, and presence of cough are all non-missing and are indicated as 'No' at OAV#1 or OAV#2, then the subject has resolution of symptoms at the respective Outcome Assessment Visit. Otherwise, resolution of symptoms is missing at the Outcome Assessment Visit.

6.5.4. Most Severe Solicited Event at OAV#1 and OAV#2

The maximum severity at OAV #1 will be calculated based on the following rules:

- If a subject has missing data for the severity grade of any solicited event for two consecutive days or has missing data for more than two days from Day 1 to Day 5 then the most severe solicited event at OAV#1 will be missing.
- Otherwise if a subject has missing data for one or two non-consecutive days from Day 1 to Day 5 then the missing severity will be imputed as the maximum severity grade taken across the previous day and the day after the day with a missing severity. As a special case, for subjects missing severity for Day 1, the missing severity will be imputed as the Severity from Day 2. For subjects missing severity at Day 5 but not missing severity at Day 6, the missing severity will be imputed as the maximum of severity gradings from Day 4 and Day 6. For these subjects with severity grades (0 to 3) recorded or imputed for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 5, inclusive, the most severe solicited event at OAV#1

will be the maximum severity grade taken across all solicited events from Day 1 to Day 5.

- If a subject had any solicited event of severity grade 3 from Day 1 to Day 5, then the most severe solicited event at OAV#1 will be grade 3, regardless of the presence of missing data during that period.

In a similar manner, the maximum severity at OAV #2 will be calculated based on the following rules:

- If a subject has missing data for the severity grade of any solicited event for more than three consecutive days or has missing data for more than five days from Day 1 to Day 18 then the most severe solicited event at OAV#2 will be missing.
- Otherwise if a subject has missing data for five days or less and no more than three of them are consecutive Day 1 to Day 18 then the missing severity will be imputed as the maximum severity grade taken across the previous day and the day after the day with a missing severity. As a special case, for subjects missing severity for Day 1, the missing severity will be imputed as the Severity from Day 2. For subjects missing severity at Day 18, the missing severity will be imputed as the severity from Day 17. For these subjects with severity grades (0 to 3) recorded or imputed for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 18, inclusive, the most severe solicited event at OAV#2 will be the maximum severity grade taken across all solicited events from Day 1 to Day 18.
- If a subject had any solicited event of severity grade 3 from Day 1 to Day 18, then the most severe solicited event at OAV#2 will be grade 3, regardless of the presence of missing data during that period.

6.5.5. Ordinal Clinical Response at OAV#1 or OAV#2

If the subject died at any point of study participation, then OCR at OAV#1 will be 8.

Else if the subject has missing ACR at OAV#1 then OCR at OAV#1 will be missing.

Else if the subject did not have ACR at OAV#1 and was hospitalized from Day 1 to Day 5 then OCR at OAV#1 will be 7.

Else if the subject did not have ACR at OAV#1 and was not hospitalized from Day 1 to Day 5 then OCR at OAV#1 will be 6.

Else if the subject has missing resolution of symptoms at OAV#1 then OCR at OAV#1 will be missing.

Else if the subject did not have resolution of symptoms at OAV#1 then OCR at OAV#1 will be 5.

Else if the subject has missing most severe solicited event at OAV#1 then OCR at OAV#1 will be missing.

Else if the subject had a most severe solicited event of grade 3 at OAV#1 then OCR at OAV#1 will be 4.

Else if the subject had a most severe solicited event of grade 2 at OAV#1 then OCR at OAV#1 will be 3.

Else if the subject had a most severe solicited event of grade 1 at OAV#1 then OCR at OAV#1 will be 2.

Else OCR at OAV#1 will be 1.

If the subject died at any point of study participation, then OCR at OAV#2 will be 8.

Else if the subject has missing ACR at OAV#2 then OCR at OAV#2 will be missing.

Else if the subject did not have ACR at OAV#2 and was hospitalized from Day 1 to Day 18 then OCR at OAV#2 will be 7.

Else if the subject did not have ACR at OAV#2 and was not hospitalized from Day 1 to Day 18 then OCR at OAV#2 will be 6.

Else if the subject has missing resolution of symptoms at OAV#2 then OCR at OAV#2 will be missing.

Else if the subject did not have resolution of symptoms at OAV#2 then OCR at OAV#2 will be 5.

Else if the subject has missing most severe solicited event at OAV#2 then OCR at OAV#2 will be missing.

Else if the subject had a most severe solicited event of grade 3 at OAV#2 then OCR at OAV#2 will be 4.

Else if the subject had a most severe solicited event of grade 2 at OAV#2 then OCR at OAV#2 will be 3.

Else if the subject had a most severe solicited event of grade 1 at OAV#2 then OCR at OAV#2 will be 2.

Else OCR at OAV#2 will be 1.

Note that in some cases OCR can be defined even if some components are missing. For instance, if a subject had record of receipt of study product and did not have adequate clinical response at OAV#1, OCR at OAV#1 would still be defined even if most severe solicited event at OAV#1 was missing.

6.5.6. Number of Days of Antibiotic Use at OAV#1 or OAV#2

It will be assumed that all subjects have precisely five days of antibiotic use with the initial antibiotic prior to Day 1 (the day of the first dose of study product). Analysis involving comparisons of the number of days of antibiotic use will consider antibiotic use from Day 1 onwards. The number of days of antibiotic use is defined as the actual number of days of antibiotic use (any amount of study product that is not placebo, or any amount of other systemic antibiotic) from Day 1 to Day 5, inclusive, for OAV#1 and from Day 1 to Day 18 for OAV#2. For subjects that received placebo as study product, it is counted as the number of days of systemic antibiotic as determined solely from the concomitant medication form. For subjects that receive actual antibiotic as study product, it is counted as the number of days that the subject received any amount of either study product or a non-study systemic antibiotic, as determined

from the concomitant medication form. Note that missed doses of study product do not necessarily lower the number of days of antibiotic use as long as a separate dose of antibiotic (study product antibiotic or concomitant medication antibiotic) was received on that day. Extra doses of study product beyond the protocol specification of 10 doses count as normal toward the number of days of antibiotic use. The number of days of antibiotic use is missing (at both OAV#1 and OAV#2) if the product administration record was not completed / on record for the subject and the subject did not have antibiotic use during the study period recorded as a concomitant medication. If a subject does not have an OAV#1 or OAV#2, then number of days of antibiotic use at OAV#1 is missing. If a subject does not have an OAV#2, then number of days of antibiotic use at OAV#2 is missing. As exceptions, subjects that were hospitalized due to pneumonia or a complication of pneumonia or the died during the study period will have number of days of antibiotic use at OAV#1 or OAV#2 as 5 if randomized to the standard course or as 0 if randomized to short course if the number of days of antibiotic use at OAV#1 or OAV#2 is missing as defined above.

The number of days of antibiotic use at the time of analysis will be determined from the product administration records and concomitant medication records only. Data management activities and site queries (outside the scope of this document) prior to data lock will ensure concomitant medication records are as complete as possible and consistent with other records (i.e., AEs and medically attended visit records in the clinical database). The number of days of antibiotic use for a concomitant medication will be calculated as the medication end date minus the medication start date plus one day. Days will not be double counted if multiple systemic antibiotics (including antibiotic as study product) are taken on the same day. Systemic antibiotic use will not be counted for days that fall outside of the range being considered (Days 1 to Day 5, or Day 1 to Day 18).

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

6.5.7. Desirability of Outcome Ranking (DOOR) at OAV#1 or OAV#2

DOOR at OAV#1 is defined by ranking all subjects (pooling together both treatment arms) according to OCR at OAV#1 (lower is better) and using the number of days of antibiotic use at OAV#1 (lower is better) as a tie-breaker for comparing the ranking of two subjects with the same OCR. DOOR at OAV#2 is defined by ranking all subjects (pooling together both treatment arms) according to OCR at OAV#2 (lower is better) and using the number of days of antibiotic use at OAV#2 (lower is better) as a tie-breaker for comparing the ranking of two subjects with the same OCR. DOOR at OAV#1 or at OAV#2 is missing only if OCR or number of days of antibiotic use is missing for the respective OAV.

The ranking algorithm for DOOR is implemented as follows. A score variable is created that adds the number of days of antibiotic use (as defined in Section 6.5.6) divided by 100 to the OCR. Subjects are then ranked (DOOR) by the score, with the highest rank going to the subject with the lowest score, and the lowest rank going to the subject with the highest score. Tied scores result in a DOOR equal to the mean of the tied ranks. The algorithm is exemplified below using a simple scenario with 4 subjects.

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

6.6. Interim Analyses and Data Monitoring

One interim analysis, described below, will be performed by the SDCC statistician responsible for this protocol and reported to the DSMB after approximately 30% of the targeted subjects have completed the study. The interim analysis will inform DSMB decisions regarding stopping early for efficacy, futility, or safety. Only the SDCC statistician and the DSMB will see the interim analysis report.

For the interim analysis, a snapshot of the study database will be unblinded and used to conduct analyses as follows. An ITT analysis including all enrolled subjects in the snapshot of the study database will be performed, testing the null hypothesis (H0: Probability of higher DOOR in short course + ½ probability of equal DOOR = 0.5) using the methods described in Section 8.1.1, with the modification that the Haybittle-Peto boundary ($p<0.001$) will be used when concluding statistical significance. The study may be stopped early for efficacy only if statistical significance is detected in that test. In the event of statistical significance, sensitivity analyses using complete case and according-to-protocol cohorts (CC-V1 and ATP-V1, as described below) as well as worst case analyses will be included in the DSMB report to further guide decisions for stopping for efficacy.

A 95% confidence interval for the probability that a randomly selected subject will have a better DOOR if assigned to the 5-day strategy (vs. the standard strategy) will be estimated but not used to inform DSMB decisions about stopping early for efficacy. Predicted interval plots (PIPS, Section 6.6.1) will be constructed to provide the DSMB with a prediction of the trial results were the trial to continue as planned under varying assumptions regarding future data (e.g., current trend continues, null hypothesis is true, alternative hypothesis is true). In order to assess whether the 5-day strategy is differentially effective in subgroups of subjects, 95% confidence intervals for the probability of higher DOOR (as well as p-values for the test of a probability of higher DOOR of 0.5) when assigned to the short course of antibiotics will be shown as forest plots comparing each stratification variable (age <2 years, age ≥2 years, ED as the initial treatment site, out-patient or urgent care as the initial treatment site, amoxicillin as the initial antibiotic, amoxicillin-clavulanate as initial antibiotic, and cefdinir as initial antibiotic).

The DSMB will also be provided with the following:

1. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a between arm difference in the overall outcome (DOOR) via a cumulative difference plot with respective confidence bands for Outcome Assessment Visit #1.
2. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics at Outcome Assessment Visit #1.
3. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) Oral, rectal, axillary or tympanic temperature ≥38.3˚C (100.9˚F), confirmed by repeat measurement after at least 15 minutes, in the 24 hours preceding Outcome Assessment Visit #1 or measured at the assessment visit, unless attributed to a new process that is unrelated to the prior diagnosis of pneumonia; (2) Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at Outcome Assessment Visit #1, and (3) Presence of cough Grade 2 or 3 at Outcome Assessment Visit #1.
4. For subjects that have completed Outcome Assessment Visit #1 and have received at least one dose of study product, a forest plot of 95% confidence intervals for the risk difference of each solicited event and with the risk difference of any solicited event, for each severity threshold (mild or greater, moderate or greater, or severe) for Outcome Assessment Visit #1.

The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

6.6.1. Predicted Interval Plots (PIPs)

PIPs provide insight into the range of possible outcomes that can be expected for the final primary analysis under various assumptions (such as that the current observed treatment effect represents the true effect or that the null hypothesis represents the true effect). Using various assumptions, data is simulated from theoretical distributions to create multiple complete datasets representing complete datasets for the final analysis under the assumed reality. Details of PIPs and their interpretations can be found in the literature (Evans 2007, Li 2009).

For each assumption, one-hundred (100) 95% predicted intervals of the probability of higher DOOR in the 5-day treatment course at Outcome Assessment Visit #1 will be generated from 100 complete datasets. Each dataset will include the ITT analysis population for the interim analysis, plus additional simulated subjects to a total of 400 subjects in the dataset. Predicted intervals will be computed by inverting the Mann-Whitney U test (Section 8.2.2). The predicted intervals will be ordered by their corresponding point estimate of the probability of higher DOOR in the 5-day treatment course and shown graphically as forest plots. The 95% confidence interval generated in the ITT interim analysis of the probability of higher DOOR at Outcome Assessment Visit #1 will be overlaid on the forest plot. Comparisons of the predicted intervals to

the confidence interval show changes in precision of estimated probability (tightness of predicted intervals versus the confidence interval) as well as the expected distribution of location shifts of the estimated probability in the final analysis relative to the interim analysis, dependent on the assumptions used. Conditional power will be estimated as the percentage of predicted intervals with a lower bound that is greater than 0.5.

Three assumptions will be included in the PIPs: 1) current trend, 2) null hypothesis, and 3) alternative hypothesis. Further assumptions may be explored depending on results of the ITT analysis of the primary endpoint but will not be pre-specified.

Under the current trend assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the empirical distribution of DOOR values by treatment from the same dataset.

Under the null hypothesis assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the overall (not by treatment) empirical distribution of DOOR values from the same dataset.

Under the alternative hypothesis assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the overall (not by treatment) empirical distribution of DOOR values from the same dataset. All simulated subjects with a treatment assignment randomly chosen as the 5-day course will have the DOOR (rank) shifted by a value beta. The value beta will be chosen through a manual trial-and-error process such that the probability of higher DOOR in the 5-day subjects, comparing simulated subjects only, has a mean value of approximately 0.6 across all 100 datasets.

6.7. Multicenter Studies

This is a multicenter study. Because there are twelve strata prior to considering site, further stratification by site would result in an excessive number of strata and so randomization is not stratified by site. Therefore, treatment imbalances might by chance occur within sites. Additionally, the potential for site effects on DOOR components is present. Therefore, sensitivity analyses for potential site effects are necessary.

In the primary analysis, data will be pooled across all clinical sites and analyses will not adjust for potential site effects. However, as a sensitivity analysis, the ITT analysis of DOOR at Outcome Assessment Visit #1 will be repeated as a stratified analysis in which each site will be analyzed separately (see Section 8.3.2).

6.8. Multiple Comparisons/Multiplicity

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

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Reasons for screening failures will be summarized in Table 8. The completion status and reasons for early termination or treatment discontinuation will be summarized (Table 4 and Listing 1). A subject could be discontinued early due to an AE (serious or non-serious), loss to follow-up, non-compliance with study, voluntary withdrawal by parent/guardian, withdrawal at the investigator request, termination of the site by the sponsor, termination of the study by the sponsor, death, lack of eligibility at enrollment, or becoming ineligible after enrollment.

Subject disposition and eligibility for analysis will be summarized in a CONSORT flow diagram (Figure 2).

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 2 and Listing 2). Non-subject specific protocol deviations will be in Listing 3. All subject-specific protocol deviations and non subject-specific protocol deviations will be presented. Major protocol deviations (see Section 6.3.3) will be discussed.

8. EFFICACY EVALUATION

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

All statistical tests are two-sided and performed at the α=0.05 significance level.

8.1. Primary Efficacy Analysis

The primary efficacy analyses will be performed for the ITT cohort.

8.1.1. Primary Analysis of DOOR at Outcome Assessment Visit #1

DOOR at Outcome Assessment Visit #1 is defined in Section 3.3.

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

> H0: The sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR at Outcome Assessment Visit #1 than if assigned to the 10-day arm plus one-half the probability of equal DOORs at Outcome Assessment Visit #1 is 50% (i.e., no difference in DOOR at Outcome Assessment Visit #1).

The above null hypothesis can be tested using a Mann-Whitney U Test (Evans 2015).

The primary analysis will use multiple imputation with a linear model to impute missing DOOR at Outcome Assessment Visit #1 outcomes. Details of multiple imputation methods are described in Section 8.4.1.

For each of the 20 complete multiply imputed datasets, a Mann-Whitney U statistic will be computed using randomization to short course versus randomization to standard course to define the binary grouping and DOOR at Outcome Assessment Visit #1 as the outcome. The U statistics are asymptotically normal distributed, and so they can be combined into a single test statistic using Rubin's Rules (Marshall 2009).

Defining the following:

n_1: number of subjects in ITT cohort randomized to a short course of antibiotics

n_2: number of subjects in ITT cohort randomized to a standard course of antibiotics

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

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

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

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

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

$$\bar{U} = \mathrm{Var}(Q_i) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \sum_{c=1}^{D}(M_c^3 - M_c)\right]$$ (Lehmann 1975, Zhao 2008),

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

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

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

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

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

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

Under null hypothesis corresponding to the primary analysis of this study,

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

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

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

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

A point estimate of the probability will be obtained by dividing $\bar{Q}$ by $n_1 n_2$. Results will be shown in Table 14.

8.2. Secondary Efficacy Analyses

8.2.1. Analysis of DOOR at Outcome Assessment Visit #2, Performed as ITT in an Analogous Manner to the Primary Analysis

DOOR at Outcome Assessment Visit #2 is defined in Section 3.3.

The null hypothesis corresponding to this analysis is:

> H0: The sum of the probability that a subject assigned to the 5-day arm will have a higher DOOR at Outcome Assessment Visit #2 than if assigned to the 10-day arm plus one-half the probability of equal DOORs at Outcome Assessment Visit #2 is 50% (i.e., no difference in DOOR at Outcome Assessment Visit #2).

The above null hypothesis can be tested using a Mann-Whitney U Test (Evans 2015).

This analysis will use multiple imputation with a linear model to impute missing DOOR at Outcome Assessment Visit #2 outcomes. Details of multiple imputation methods are described in Section 8.4.1.

For each of the 20 complete multiple imputation datasets, a Mann-Whitney U statistic will be computed using randomization to short course versus randomization to standard course to define the binary grouping and DOOR at Outcome Assessment Visit #2 as the outcome. The U statistics are asymptotically normal distributed, and so they can be combined into a single test statistic using Rubin's Rules (Marshall 2009).

Defining the following:

n_1: number of subjects in ITT cohort randomized to a short course of antibiotics

n_2: number of subjects in ITT cohort randomized to a standard course of antibiotics

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

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

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

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

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

$$\bar{U} = \text{Var}(Q_i) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \sum_{c=1}^{D}(M_c^3 - M_c)\right]$$ (Lehmann 1975, Zhao 2008),

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

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

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

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

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

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

Under null hypothesis corresponding to the primary analysis of this study,

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

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

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

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

A point estimate of the probability will be obtained by dividing $\bar{Q}$ by $n_1 n_2$. Results will be shown in Table 15.

8.2.2. Sensitivity Analyses for the DOOR at Outcome Assessment Visits #1 and #2 ITT analyses.

In addition to the ITT analysis of the DOOR at Outcome Assessment Visits #1 and #2, analyses using alternative analysis populations or imputation strategies will be performed: (1) CC analyses. (2) ATP analyses. (3) Worst case analyses. All of these analyses will test the null hypotheses described in Section 8.1.1 and Section 8.2.1 using the Mann-Whitney U Test, estimate Pr(Higher DOOR in short course) + 0.5 Pr(Equal DOOR) using U divided by the number of pairwise comparisons, and will compute confidence intervals by (1) inverting the Mann-Whitney U Test and (2) using a non-parametric bootstrap. Results will be shown in Table 16 and Table 17 for Outcome Assessment Visits #1 and #2, respectively.

Confidence intervals from inverting the Mann-Whitney U Test:

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

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

$$\text{Var}(U) = \frac{n_1 n_2}{12}\left[(n_1 + n_2 + 1) - \sum_{c=1}^{D}(M_c^3 - M_c)\right] \quad \text{(Lehmann 1975, Zhao 2008),}$$

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

Confidence intervals using a non-parametric bootstrap:

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

Where $U_{0.025}$ and $U_{0.975}$ are chosen as the 250$^{\text{th}}$ and 9750$^{\text{th}}$ values in a sorted array of 10,000 values of Mann Whitney U statistics generated from random resampling (number of values sampled to generate the statistic will be equal to the number of subjects in the respective analysis population) of the empirical distributions of DOOR scores in each treatment arm for the given analysis population.

8.2.2.1. Complete Case Analysis of the DOOR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.2 using the CC-V1 population. Ordinal clinical response values, number of days of antibiotic use, and DOOR at outcome assessment visit #1 of CC-V1 subjects will be presented in Listing 19.

8.2.2.2. Complete Case Analysis of the DOOR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.2 using the CC-V2 population. Ordinal clinical response values, number of days of antibiotic use, and DOOR at outcome assessment visit #2 of CC-V2 subjects will be presented in Listing 19.

8.2.2.3. According-to-Protocol Analysis of the DOOR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.2 using the ATP-V1 population.

8.2.2.4. According-to-Protocol Analysis of the DOOR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.2 using the ATP-V2 population.

8.2.2.5. Worst Case Analysis of the DOOR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.2 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8 and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 0. As an exception, subjects in the short course arm with OCR missing for Outcome Assessment Visit #1 but not for Outcome Assessment Visit #2 will have the OCR for Outcome Assessment Visit #1 imputed as the Outcome Assessment Visit #2 value or as 5, whichever value is larger. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.) and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 5.

8.2.2.6. Worst Case Analysis of the DOOR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.2 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8 and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 0. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.) and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 5.

8.2.3. Solicited Events at Outcomes Assessment Visits #1 and #2

Separately for Outcome Assessment Visit #1 and #2, using CC-V1 and CC-V2, respectively, a forest plot of 95% confidence intervals for the risk difference of each solicited event and the risk difference of any solicited, for each severity threshold (mild or greater, moderate or greater, or severe) will be produced (Figure 3, Figure 4, Figure 5 and Figure 6, Figure 7, Figure 8). Results will also be reported in tables (Table 18, Table 19, Table 20, Table 21, Table 22, and Table 23), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

8.2.4. Resolution of Symptoms at Outcomes Assessment Visits #1 and #2

Separately for Outcome Assessment Visit #1 and #2, using CC-V1 and CC-V2, respectively, a forest plot of 95% confidence intervals for the risk difference of lack of resolution of symptoms as well as the following: (1) fever (as defined in Section 6.5.2) (2) Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit; and (3) Presence of cough Grade 2 or 3 at the Outcome Assessment Visit will be given (Figure 9 and Figure 10). Results will also be reported in tables (Table 24 and Table 25), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

8.2.5. Adequate Clinical Response at Outcomes Assessment Visits #1 and #2

Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of adequate clinical response as well as the following interventions for persistent or worsening pneumonia: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics will be given (Figure 11 and Figure 13). Results will also be reported in tables (Table 26 and Table 28), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

Separately for Outcome Assessment Visit #1 and #2, using CC cohorts, a forest plot of 95% confidence intervals for the risk difference of the following interventions for any reason: (1) ED/clinic visits, (2) hospitalizations, (3) surgical procedures, and (4) non-study systemic antibiotics will be given (Figure 12 and Figure 14). Results will also be reported in tables (Table 27 and Table 29), and tests for differences in proportions between treatment arms will be given by Fisher's exact tests. The Newcombe method with continuity correction will be used to compute all 95% confidence intervals for risk differences.

8.2.6. Ordinal Clinical Response at Outcomes Assessment Visits #1 and #2

Analysis of the ordinal clinical response (OCR) at Outcome Assessment Visits #1 and #2. Separately for OCR at each of the two visits, a first ITT analysis (superiority/inferiority) will test the null hypothesis that

$$\Pr(\text{OCR is better in short course}) + 0.5 \Pr(\text{OCR is equal}) = 0.5.$$

A second ITT analysis (non-inferiority) will test the null hypothesis that

$$\Pr(\text{OCR is better in short course}) + 0.5 \Pr(\text{OCR is equal}) < 0.4.$$

ITT, CC, ATP, and worst case analyses will plot cumulative difference plots and test whether the overall distributions of OCR are equivalent between the treatment arms for OCR at each of the two visits.

Cumulative difference plots (Figure 15, Figure 16, Figure 17, Figure 18 and Figure 19, Figure 20, Figure 21, Figure 22) are produced as follows. For $i \in \{1,2,3,4,5,6,7\}$, the difference in proportions of subjects with $\text{OCR} \leq i$ between treatment arms is plotted (i on x-axis and

difference in proportion on y-axis), together with 95% confidence intervals computed using the Newcombe method with continuity correction.

For CC-V1, CC-V2, ATP-V1, and ATP-V2 analysis populations, OCRs will be summarized by treatment group and tests of overall distributions of OCR will be performed using the mean score statistic (QS). The mean score statistic is obtained from PROC FREQ in SAS using the "chisq" option and is denoted in output as the "Mantel-Haenszel Chi-Square" statistic.

8.2.6.1. ITT Analyses of OCR at Outcomes Assessment Visit #1

Twenty (20) multiple imputation datasets for OCR at Outcome Assessment Visit #1 will be generated in manner analogous to that described in Section 8.1.1, except using OCR at Outcome Assessment Visit #1 in place of DOOR at Outcome Assessment Visit #1 for the response. Also, analogous to Section 8.1.1, the Mann-Whitney U statistic will be computed for each of the datasets and combined using Rubin's Rules to generate the test statistic W and a p-value for the test of the null hypothesis that

Pr(OCR at Outcome Assessment Visit #1 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5.

The F-test using the W statistic will be inverted to produce a 95% confidence interval for Pr(OCR is better in short course) + 0.5 Pr(OCR is equal). Whether the lower bound of this confidence interval is greater than 0.4 will serve as a test of the non-inferiority null hypothesis that

Pr(OCR at Outcome Assessment Visit #1 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) < 0.40.

Results will be reported in Table 30.

8.2.6.2. ITT Analyses of OCR at Outcomes Assessment Visit #2

Twenty (20) multiple imputation datasets for OCR at Outcome Assessment Visit #2 will be generated in manner analogous to that described in 8.2.1, except using OCR at Outcome Assessment Visit #2 in place of DOOR at Outcome Assessment Visit #2 for the response. Also, analogous to 8.2.1, the Mann-Whitney U statistic will be computed for each of the datasets and combined using Rubin's Rules to generate the test statistic W and a p-value for the test of the null hypothesis that

Pr(OCR at Outcome Assessment Visit #2 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5.

The F-test using the W statistic will be inverted to produce a 95% confidence interval for Pr(OCR is better in short course) + 0.5 Pr(OCR is equal). Whether the lower bound of this confidence interval is greater than 0.4 will serve as a test of the non-inferiority null hypothesis that

Pr(OCR at Outcome Assessment Visit #2 is better in short course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) < 0.40.

Results will be reported in Table 31.

8.2.6.3. Complete Case Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the CC-V1 population. Results will be reported in Table 32 and Table 33.

8.2.6.4. Complete Case Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the CC-V2 population. Results will be reported in Table 34 and Table 35.

8.2.6.5. According-to-Protocol Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the ATP-V1 population. Results will be reported in Table 36 and Table 37.

8.2.6.6. According-to-Protocol Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the ATP-V2 population. Results will be reported in Table 38 and Table 39.

8.2.6.7. Worst Case Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8. As an exception, subjects in the shorts course arm with OCR missing for Outcome Assessment Visit #1 but not for Outcome Assessment Visit #2 will have the OCR for Outcome Assessment Visit #1 imputed as the Outcome Assessment Visit #2 value or as 5, whichever value is larger. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.). Results will be reported in Table 40.

8.2.6.8. Worst Case Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.). Results will be reported in Table 41.

8.2.7. Additional Analysis of Cough

The proportion of subjects in each treatment group experiencing moderate or severe cough will be tabulated by day from Day 1 to Day 25 (as recorded from the memory aid), by visit, and overall, with 95% exact confidence intervals (Table 42). The proportion of subjects in each treatment group experiencing cough will also be tabulated by day from Day 1 to Day 25 (as recorded from the memory aid), by visit, and by severity level (Table 43 and Table 44). Finally, cough will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) (Table 45). Proportions for these derived binary variables will be reported along with 95% exact confidence intervals. Comparisons of proportions by treatment groups will be given as odds ratios (with

95% exact confidence intervals) and p-values from Fisher's Exact Tests. Cough severity will be listed by study day and study visit (Listing 15 and Listing 16).

8.3. Exploratory Efficacy Analyses

8.3.1. Complete Case Evaluation of DOOR at Outcome Assessment Visit #1, Minimum Required Difference in Days for Antibiotic Use "Tie-breaking" Varies k=1,2,3,4,5, or infinity

In the primary RADAR/DOOR analysis, if two subjects from separate treatment arms have an equal ordinal clinical response but a difference in the duration of antibiotic use of at least k=1 day, RADAR assigns a more favorable response to the subject with fewer days of antibiotic use. For a sensitivity analysis, the effect of increasing the minimum difference in the duration of antibiotic use (k=2,3,4, or 5, or infinity) before a favorable response is given to the subject with shorter duration of antibiotic use will be explored. The analysis of RADAR/DOOR with k=infinity is equivalent to comparison of OCR without regard for number of days of antibiotic use, and is included here for comparative purposes. For each value of k, bootstrapped confidence intervals of the probability of more favorable DOOR due to assignment to the 5-day antibiotic course will be computed and plotted versus k. Analysis will be performed separately for DOOR at Outcome Assessment Visit #1 and DOOR at Outcome Assessment Visit #2. Analyses will be performed using CC-V1/CC-V2 cohorts. Results will be reported in Table 46 and Figure 23.

8.3.2. Stratified (ITT) Analyses of DOOR at Outcome Assessment Visit #1

Analysis of DOOR at Outcome Assessment Visit #1 as described in Section 8.1.1 will be performed separately for each level of each stratification variable (e.g. an analysis of all subjects of age <24 months at enrollment, and a separate analysis of all subjects of age 24-71 months at enrollment) and by clinical site. Results will be reported Table 47.

8.3.3. As Treated Analysis of Effect of Number of Days of Antibiotic Use on OCR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

The analysis will be performed using the subset of the CC-V1 analysis population that did not receive off-study systemic antibiotic unrelated to pneumonia prior to Outcome Assessment Visit #1. The justification for excluding subjects with unrelated antibiotic use is that subjects receiving unrelated antibiotics are at risk for both improved outcomes due to ongoing antibiotic use as well as increased side effects related to antibiotics administration. The effect of the number of days of antibiotic use at Outcome Assessment Visit #1 on OCR at Outcome Assessment Visit #1 will be analyzed using a proportional odds model that simultaneously uses all cumulative logits (Agresti 2003).

Let **K** be the set of distinct OCR values observed at Outcome Assessment Visit #1, with the exception that the highest (worst) distinct value observed is not included in the set.

Let Y_i = the OCR of subject i at Outcome Assessment Visit #1.

Let X_i = the number of days of antibiotic use at Outcome Assessment Visit #1 for subject *i*.

α_k, where k ϵ K, and β are parameters to be simultaneously estimated through maximum likelihood methods.

Then, proportional odds model with cumulative logits is defined as

$\text{Logit}\,[P(Y_i > k)] = \alpha_k + \beta X_i\,, \qquad k \in \mathbf{K}$

The following gives the interpretation of the model. Suppose D is any non-negative integer.

Then, $\log[\text{odds}(OCR>k \mid X_i = D+1) / \text{odds}(OCR>k \mid X_i = D)] = \beta$.

That is, for any *k*, where *k* is from the set of observed OCR values at Outcome Assessment Visit #1 besides the highest observed value, e^{β} gives the odds ratio of an OCR at Outcome Assessment Visit #1 greater than *k* for the effect of one additional day of use of antibiotic.

It should be stated clearly that this analysis is "as treated" rather than "as randomized." As such, causality cannot be inferred from a statistically significant association. This is especially true if subjects receiving off-study antibiotic not unrelated to the prior diagnosis of pneumonia are observed during the study. Such subjects will have a higher OCR and will also likely have more days of antibiotic use.

This analysis will be repeated using the subset of the CC-V2 analysis population that did not receive off-study systemic antibiotic unrelated to pneumonia prior to Outcome Assessment Visit #2. The effect of the number of days of antibiotic use at Outcome Assessment Visit #2 on OCR at Outcome Assessment Visit #2 will be analyzed using logistic regression with a proportional odds assumption. Results from both analyses will be summarized in Table 48. The odds ratio for the proportional odds of an OCR at Outcome Assessment Visit #1 greater than k for the effect of one additional day of use of antibiotic will be reported with a 95% Wald confidence interval and p-value from a Wald test. For $p<0.05$, an association between OCR and the number of days of antibiotic use, as treated, will be concluded.

8.4. Imputation of Missing Data

8.4.1. Multiple Imputation of Missing Ordinal Clinical Response and DOOR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

Several analyses, including the primary analysis, depend on multiple imputation of DOOR or OCR at Outcome Assessment Visit #1 or Outcome Assessment Visit #2. Multiple imputations of each of these missing endpoints will be performed independently, and each subject will have their missing endpoints imputed independently of other subject's imputations using a subject-specific imputation model.

As a first step to multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for DOOR at Outcome Assessment Visit #1 and OCR at Outcome Assessment Visit #1 is below.

- Indicator of subject enrolled at the site with the second most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the third most number of subjects enrolled (binary indicator)

- Indicator of subject enrolled at the site with the least number of subjects enrolled (binary indicator)
  - Note: the site with the most number of subjects enrolled is reference for site. Language is written to allow for an arbitrary number of sites. In the event of a number of ties for the number of subjects enrolled, tied sites will be ordered in ascending alphanumeric order in the list of model variables.
- Indicator of amoxicillin (not amoxicillin placebo) as study treatment (binary indicator)
- Indicator of amoxicillin-clavulanate (not amoxicillin-clavulanate placebo) as study treatment (binary indicator)
- Indicator of cefdinir (not cefdinir placebo) as study treatment (binary indicator)
  - Note: placebo is the reference group for study treatment
- Indicator for amoxicillin-clavulanate as initial antibiotic (binary indicator)
- Indicator for cefdinir as initial antibiotic (binary indicator)
  - Note: amoxicillin is the reference group for initial antibiotic
- Indicator for age $\geq$ 2 years at enrollment (binary indicator)
- Indicator for initial treatment site for pneumonia at an emergency department (binary indicator)
- OCR at Outcome Assessment Visit #2 (imputed OCRs will not be used)
- Severity of cough on Day 1 as recorded on Solicited Events form (0, 1, 2, or 3)
  - Note: amoxicillin is the reference group for initial antibiotic
- Severity of most severe solicited event (besides cough) on Day 1(0, 1, 2, or 3)
  - Note: Some missing values for Day 1 will first be imputed as described in Section 6.5.4
- Severity of cough on Day 2 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 2 (0, 1, 2, or 3)
  - Note: Some missing values for Day 2 will first be imputed as described in Section 6.5.4
- Severity of cough on Day 3 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 3 (0, 1, 2, or 3)
  - Note: Some missing values for Day 3 will be first imputed as described in Section 6.5.4
- Severity of cough on Day 4 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 4 (0, 1, 2, or 3)
  - Note: Some missing values for Day 4 will first be imputed as described in Section 6.5.4

- Severity of cough on Day 5 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 5 (0, 1, 2, or 3)
  - Note: Some missing values for Day 5 will first be imputed as described in Section 6.5.4

For DOOR and OCR at Outcome Assessment Visit #2, the complete list of model variables is identical to the above, but with OCR at Outcome Assessment Visit #2 replaced with OCR at Outcome Assessment Visit #1. Additionally, cough severity and most severe solicited event are listed up to Day 18 rather than Day 5.

The actual list of model variables for each subject-specific imputation model will follow the ordering above but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification given in the pseudo-code and subjects must be processed in the order described in the pseudo-code. OCR will simultaneously be imputed with DOOR at each respective Outcome Assessment Visit. The pseudo-code is in terms of the Outcome Assessment Visit #1 endpoints, but the general logic is also applicable to the Outcome Assessment Visit #2 endpoints (with references to "V1" replaces with references to "V2").

```
DEFINE i=index variable for subjects having DOOR imputed.
      Subjects requiring imputation are sorted in ascending order
      by PATID.
DEFINE N=number of subjects requiring imputation
DEFINE g&i=analysis dataset containing predictors and DOOR for
       CC-V1 subjects as well as subject i (only one subject not in
       CC-V1 included).  Note that CC-V1 subjects that are missing a
       value
       for one or more variables in the subject-specific imputation
       model are excluded.
DEFINE imp_g&i = g&i, with 20 imputed values for the missing DOOR
      added by PROC MI
DEFINE &&modelVars_&i = list of observed variables in subject i, to
      be used for imputation of DOOR and OCR.


%do i=1 %to &N;
PROC MI data=g&i out=imp_g&i seed=1200&i NIMPUTE=20 noprint;
      var &&modelVars_&i DOOR OCR;
      monotone reg(DOOR_V1 = &&modelVars_&i);
      monotone reg(OCR_V1 = &&modelVars_&i);
```

```
run;
%end;


imp_g&i will be subset to contain only rows for the subjects with
imputed DOOR and merged together and with CC-V1 data to create the
twenty complete multiply imputed datasets
**********************************************************************
```

9. SAFETY EVALUATION

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

9.1. Demographic and Other Baseline Characteristics

Summaries of age, gender, enrollment site, ethnicity, race, initial antibiotic therapy, initial treatment locations, and age group (<24 months vs. 24-71 months) will be presented by site (Table 9 and Table 10) or by treatment group and overall (Table 11 and Table 12). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, a subject's guardians may designate the subject as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Summaries of subject's medical history will be presented by MedDRA® system organ class (SOC) and treatment group (Table 13).

Individual subject listings for all demographics (Listing 5) and pre-existing medical conditions (Listing 6) will be presented.

9.1.1. Concurrent Illnesses and Medical Conditions

Physical assessment findings from the enrollment visit, and any follow up visits, will be included in Listing 11.

9.1.2. Prior and Concurrent Medications

All concomitant medications taken within 30 days of signing the informed consent or during the study period will be recorded. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. A by-subject listing of concomitant medication use will be presented (Listing 12). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group (Table 56).

9.2. Measurements of Treatment Compliance

Treatment was administered to subjects at their homes by a parent or caregiver. The number of subjects receiving the first dose of study product will be tabulated by site, treatment group, and time period (Table 6). The number of doses of study product administered will be presented by treatment group (Table 7, Listing 7).

9.3. Adverse Events

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

9.3.1. Solicited Events

Solicited events will be captured daily until Outcome Assessment Visit #1; thereafter, parents/legal guardians will report symptoms based on memory aid and medical interview by study staff. For those with multiple solicited events, the ordinal response table will be based upon the most severe solicited event.

Solicited events were recorded for trial Days 1-25, or until study completion or termination, as the maximum severity for each day. Target solicited events include irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis.

The proportion of subjects in each treatment group experiencing each solicited event with mild or greater severity will be tabulated by day and overall (Table 49 and Table 50). The proportion of subjects in each treatment group experiencing each solicited event will also be tabulated by day and severity level (Table 51 and Table 52). Finally, solicited events will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) (Table 53). Proportions for these derived binary variables will be reported along with 95% exact confidence intervals. Comparisons of proportions by treatment groups will be given as odds ratios (with 95% exact confidence intervals) and p-values from Fisher's Exact Tests.

The maximum severity occurrence of each solicited event and cough (proportion of subjects for each severity level) will be plotted for each solicited adverse event (Figure 24). Solicited events by subject will also be presented (Listing 8).

9.3.2. Unsolicited Adverse Events

As the safety profile of amoxicillin, amoxicillin-clavulanate, and cefdinir are well established, and this trial is not powered to detect new, unknown safety signals, **there will be no unsolicited event collection during this study and only protocol-defined SAE's will be collected**.

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

Detailed narratives will be given for any deaths or other protocol-defined SAEs that occurred during the study. Listings of SAEs will be presented including subject ID, AE description, AE onset date/end date, reason reported as an SAE, relationship to treatment, alternate etiology if not related, outcome, and duration of event (days) (Listing 9). SAEs will also be listed in Table 54.

9.5. Vital Signs and Physical Evaluations

Vital signs will be taken at the enrollment visit, Outcome Assessment Visit #1, and Outcome Assessment Visit #2. For each visit, by treatment group, the mean, median, standard deviation, min, and max of vital sign will be calculated for temperature, respiration rate, and pulse (Table 55). Individual vital signs measurements will be listed (Listing 10).

9.6. Concomitant Medications

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

will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented. The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the Safety population (Table 56).

9.7. Other Safety Measures

The number and percent of subjects visiting an emergency department, primary care provider, study physician, urgent care, or having some other type of medically attended visit due to worsening study pneumonia will be presented together with whether the subject received antibiotic, surgical treatment, or was hospitalized due to pneumonia or a complication of pneumonia (Table 57). Medically attended visits will also be listed (Listing 13 and Listing 14). Presence of fever will be listed by visit (Listing 17 and Listing 18).

10. OTHER ANALYSES

No other analyses are planned.

11. REPORTING CONVENTIONS

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

12. TECHNICAL DETAILS

SAS version 9.3 or above or R version 3.2 or above will be used to perform analyses and to generate all tables, figures and listings.

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

Changes in the Conduct of the Study

Enrollment into the study was initiated under protocol version 2.0. Substantive changes to the protocol after study initiation are provided below.

Substantive changes in protocol version 3.0

- Removed 200mg/5mL amoxicillin and 200mg/5mL amoxicillin-clavulanate as possible dose strengths under Protocol Section 6.1.2. No subjects were prescribed under this dose.
- Clarified timing of interim analysis to be after at least 30% of the targeted subjects have completed the study instead of approximately 30%.

Changes to the Planned Analyses

There are no changes to the planned analyses as described in the protocol.

14. REFERENCES

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Zhao, Yan D., Dewi Rahardja, and Yongming Qu. "Sample size calculation for the Wilcoxon–Mann–Whitney test adjusting for ties." Statistics in medicine 27.3 (2008): 462-468.

15. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

10.2 Protocol Deviations

Table 2: Distribution of Protocol Deviations by Category, Type and Treatment Group

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

12.2.2 Displays of Adverse Events

Table 3: Solicited Adverse Event Grading Scale

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Irritability	More irritable or fussy than usual but can be consoled; no interference with smiling/playing	Irritability or fussiness that is difficult to console and interferes with smiling and playing	Irritability or fussiness that lasts for more than 4 consecutive hours in a 24 hour period or cannot be consoled
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 occurring >6 times/day	Bloody diarrhea, or diarrhea that requires medical intervention, laboratory testing, or hospitalization
Allergic Reaction	Localized rash or pruritus without rash	Diffuse rash (maculopapular or urticarial)	Generalized rash consistent with Stevens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis; anaphylaxis; or angioedema
Stomatitis	Oral lesions associated with parenteral report of mild oral discomfort	Oral lesions associated with difficulty swallowing, but able to eat and drink	Oral lesions associated with inability to swallow solids or liquids; requires medical intervention, IV fluids, or hospitalization
Candidiasis	Mild mucocutaneous candidiasis or diaper dermatitis, with no treatment or topical treatment only	Moderate mucocutaneous candidiasis requiring oral antimicrobial treatment	Severe mucocutaneous candidiasis; requires medical intervention, intravenous treatment, or hospitalization

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 4: Subject Disposition by Treatment Group

Subject Disposition	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received First Dose of Treatment	x	xx	x	xx	x	xx
Received All Scheduled Treatment[a]	x	xx	x	xx	x	xx
Completed All Future Use Sample Collection						
Completed Outcome Assessment Visit #1 (Study Day 6-10)[a]						
Completed Outcome Assessment Visit #2 (Study Day 19-25) [a]						

[a] Refer to Listing 1 for reasons subjects discontinued or terminated early.
[b] Refer to Listing 4 for reasons subjects are excluded from the Analysis populations.

Table 5: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
ITT[1]	Any Reason	x	xx	x	xx	x	xx
	Became ineligible before taking study product						
CC-V1[2]	Any Reason						
	Subject not treated with study product						
	Early termination before Outcome Assessment Visit #1						
	-Reason 1 for termination						
	-Reason 2 for termination						
	Completed Outcome Assessment Visit #1, but Missing DOOR Component						
	-Adequate Clinical Response						
	-Resolution of Symptoms						
	-Solicited Event Severity Days 1-5						
	-Number of Days of Antibiotic Use						
CC-V2	Any Reason						
	Subject not treated with study product						
	Early termination before Outcome Assessment Visit #2						
	-Reason 1 for termination						
	-Reason 2 for termination						
	Completed Outcome Assessment Visit #2, but Missing DOOR Component						
	-Adequate Clinical Response						
	-Resolution of Symptoms						
	-Solicited Event Severity Days 1-8						
	-Number of Days of Antibiotic Use						
ATP-V1[3]	Any Reason						
	The subject was excluded from CC-V1 cohort.						

Table 5: Analysis Populations by Treatment Group *(continued)*

Analysis Populations	Reason Subjects Excluded	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
	Subject did not receive at least one dose of study product each day from Day 1 to Day 5						
	Major protocol deviation						
	-Outcome Assessment Visit #1 occurred out of the protocol defined window of Day 6-10						
	-Outcome Assessment Visit #1 did not occur as an in-person visit						
ATP-V2	Any Reason						
	The subject was excluded from CC-V2 cohort.						
	Subject did not receive at least one dose of study product each day from Day 1 to Day 5						
	Major protocol deviation						
	-Outcome Assessment Visit #2 occurred out of the protocol defined window of Day 19-25						
	-Outcome Assessment Visit #2 did not occur as an in-person visit						

[1] ITT = Intent-to-Treat
[2] CC = Complete Case
[3] ATP = According-to-Protocol

Table 6: Dates of First Treatment by Site and Treatment Group

Site	Treatment Group	July 2016 - June 2017	July 2017 - June 2018	July 2018 - June 2019	July 2019 - November 2019
Children's Hospital of Philadelphia	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Children's Hospital of Pittsburgh	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Cincinnati Children's Hospital	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Duke University	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Vanderbilt University	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Any Site	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Any	Any	x	x	x	x

[Programming Note: Rows will be added for additional sites that enroll at least one subject, as needed.]

Table 7: Treatment Compliance by Treatment Group

	Number of Doses Administered n (%)												
Treatment Group	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Standard Course (N=X)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Short Course (N=X)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 8: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible[1]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x
Inclusion	Any inclusion criterion	x
	[inclusion criterion 1]	x
	[inclusion criterion 2]	x
	[inclusion criterion 3]	x
Exclusion	Any exclusion criterion	x
	[exclusion criterion 1]	x
	[exclusion criterion 2]	x
	[exclusion criterion 3]	x

[1] More than one criterion may be marked per subject.

14.1.2 Demographic Data by Study Group

Table 9: Summary of Categorical Demographic and Baseline Characteristics by Site

Demographic Category	Characteristic	Children's Hospital of Philadelphia (N=X)		Children's Hospital of Pittsburgh (N=X)		Cincinnati Children's Hospital (N=X)		Duke University (N=X)		Vanderbilt University (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Initial Antibiotic	Amoxicillin	x	x	x	x	x	x	x	x	x	x	x	x
	Amoxicillin-Clavulanate	x	x	x	x	x	x	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x	x	x	x	x	x	x

[Programming Note: Columns will be added for additional sites that enroll at least one subject, as needed.]

Table 10: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	Children's Hospital of Philadelphia (N=X)	Children's Hospital of Pittsburgh (N=X)	Cincinnati Children's Hospital (N=X)	Duke University (N=X)	Vanderbilt University (N=X)	All Subjects (N=X)
Age (Months)	Mean	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x

[Programming Note: Columns will be added for additional sites that enroll at least one subject, as needed.]

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Demographic Category	Characteristic	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x
	Female	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Initial Antibiotic	Amoxicillin	x	x	x	x	x	x
	Amoxicillin-Clavulanate	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x
Clinical Trial Site	Children's Hospital of Philadelphia	x	x	x	x	x	x
	Children's Hospital of Pittsburgh	x	x	x	x	x	x
	Cincinnati Children's Hospital	x	x	x	x	x	x
	Duke University	x	x	x	x	x	x
	Vanderbilt University	x	x	x	x	x	x

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Statistic	Standard Course (N=X)	Short Course (N=X)	All Subjects (N=X)
Age (Months)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

14.1.3 Prior and Concurrent Medical Conditions

Table 13: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

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

Note: N=Number of subjects enrolled; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy/Immunogenicity Data

Table 14: Primary ITT Analysis of DOOR at Outcome Assessment Visit #1

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx

1 Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR. Confidence interval obtained through inversion of the F-test used to compute the p-value.
2 P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 15: Primary ITT Analysis of DOOR at Outcome Assessment Visit #2

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx

1 Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal DOOR. Confidence interval obtained through inversion of the F-test used to compute the p-value.
2 P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 16: Sensitivity Analyses of DOOR at Outcome Assessment Visit #1

Analysis	Pr (Higher DOOR)[1]	Normal Approx. 95% CI[2]	Bootstrapped 95% CI[3]	P-value[4]
Complete Case (CC-V1)				
According-to-Protocol (ATP-V1)				
Worst Case (ITT)				

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR.
[2] Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance Var(U)=n1n2(n1+n2+1)/12.
[3] 2.5th and 97.5th percentiles of Pr (Higher DOOR) obtained by repeatedly re-sampling of the empirical distributions of DOOR scores by treatment arm.
[4] P-value obtained by Mann-Whitney U Test.

Table 17: Sensitivity Analyses of DOOR at Outcome Assessment Visit #2

Analysis	Pr (Higher DOOR)[1]	Normal Approx. 95% CI[2]	Bootstrapped 95% CI[3]	P-value[4]
Complete Case (CC-V2)				
According-to-Protocol (ATP-V2)				
Worst Case (ITT)				

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal DOOR.
[2] Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance Var(U)=n1n2(n1+n2+1)/12.
[3] 2.5th and 97.5th percentiles of Pr(Higher DOOR) obtained by repeatedly re-sampling of the empirical distributions of DOOR scores by treatment arm.
[4] P-value obtained by Mann-Whitney U Test.

Table 18: Risk of Mild, Moderate, or Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 19: Risk of Moderate or Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 20: Risk of Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 21: Risk of Mild, Moderate, or Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 22: Risk of Moderate or Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 23: Risk of Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 24: Lack of Resolution of Symptoms and Its Components at Outcome Assessment Visit #1 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Resolution of Symptoms									
Fever[2]									
Elevated respiratory rate[3]									
Cough[4]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of fever, elevated respiratory rate, and cough at Outcome Assessment Visit #1.
[1] P-value obtained by Fisher Exact Test.
[2] As defined in Section 6.5.2 of the SAP.
[3] Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit.
[4] Presence of cough Grade 2 or 3 at the Outcome Assessment Visit.

Table 25: Lack of Resolution of Symptoms and Its Components at Outcome Assessment Visit #2 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Resolution of Symptoms									
Fever[2]									
Elevated respiratory rate[3]									
Cough[4]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of fever, elevated respiratory rate, and cough at Outcome Assessment Visit #2.
[1] P-value obtained by Fisher Exact Test.
[2] As defined in Section 6.5.2 of the SAP.
[3] Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit.
[4] Presence of cough Grade 2 or 3 at the Outcome Assessment Visit.

Table 26: Risk of Lack of Adequate Clinical Response and Its Components from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Adequate Clinical Response									
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[3]									
Receipt of Non-Study Antibiotic[4]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
[3] For pneumonia or treatment for a complication of pneumonia, including but not limited to drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
[4] For pneumonia or treatment for a complication of pneumonia. Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

Table 27: Any Receipt of Non-Study Antibiotics and Medically Attended Visits from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[2]									
Receipt of Non-Study Antibiotic[2]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For any reason.

Table 28: Risk of Lack of Adequate Clinical Response and Its Components from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Adequate Clinical Response									
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[3]									
Receipt of Non-Study Antibiotic[4]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
[3] For pneumonia or treatment for a complication of pneumonia, including but not limited to drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
[4] For pneumonia or treatment for a complication of pneumonia. Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

Table 29: Any Receipt of Non-Study Antibiotics or Medically Attended Visit from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[2]									
Receipt of Non-Study Antibiotic[2]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For any reason.

Table 30: ITT Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 31: ITT Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 32: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (CC-V1)

Statistic	Value
CC-V1 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 33: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (CC-V1) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 34: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (CC-V2)

Statistic	Value
CC-V2 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.

[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.

[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 35: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (CC-V2) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 36: According-to-Protocol Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ATP-V1)

Statistic	Value
ATP-V1 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
Test No Difference in OCR, P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 37: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ATP-V1) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 38: According-to-Protocol Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ATP-V2)

Statistic	Value
ATP-V2 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 39: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ATP-V2) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 40: Worst Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ITT Cohort)

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
Test No Difference in OCR, P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 41: Worst Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ITT Cohort)

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 42: Number and Percentage of Subjects Experiencing Moderate or Severe Cough by Day and Treatment Group

	Standard Course - Moderate or Severe Cough				Short Course - Moderate or Severe Cough			
Study Day or Visit	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**
Overall	x	x	x	(x, x)	x	x	x	(x, x)
OAV #1	x	x	x	(x, x)	x	x	x	(x, x)
OAV #2	x	x	x	(x, x)	x	x	x	(x, x)
Day 1	x	x	x	(x, x)	x	x	x	(x, x)
Day 2	x	x	x	(x, x)	x	x	x	(x, x)
Day 3	x	x	x	(x, x)	x	x	x	(x, x)
Day 4	x	x	x	(x, x)	x	x	x	(x, x)
Day 5	x	x	x	(x, x)	x	x	x	(x, x)
Days 6-9	x	x	x	(x, x)	x	x	x	(x, x)
Day 10-13	x	x	x	(x, x)	x	x	x	(x, x)
Day 14-18	x	x	x	(x, x)	x	x	x	(x, x)
Day 19-25	x	x	x	(x, x)	x	x	x	(x, x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 43: Number and Percentage of Subjects Experiencing Coughing by Maximum Severity and Treatment Group – Standard Course

Severity	Standard Course								
	Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 44: Number and Percentage of Subjects Experiencing Coughing by Maximum Severity and Treatment Group – Short Course

Severity	Short Course								
	Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 45: Number and Percentage of Subjects Experiencing Cough of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group

Severity	Standard Course (N=X)		Short Course (N=X)		Odds Ratio (95% CI)	P-Value
	n (%)	95% CI	n (%)	95% CI		
Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

Table 46: CC-V1 Evaluation of DOOR at Outcome Assessment Visit #1, Minimum Required Difference in Days for Antibiotic Use "Tie-Breaking" Varies k=1,2,3,4,5, or Infinity

k	Pr(Higher DOOR)[1]	95% CI	P-value
1	x.x	(x.x – x.x)	x.x
2			
3			
4			
5			
∞			

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR

Table 47: ITT Evaluation of DOOR at Outcome Assessment Visit #1, Analysis By Stratification Variable and Clinical Site

Variable	Level	Pr(Higher DOOR)[1]	95% CI	P-value
Age (Months)	<24	x.x	(x.x – x.x)	x.x
	24-71			
Initial Site of Treatment	ED			
	Out-Patient / Urgent Care			
Initial Antibiotic	Cefdinir			
	Amoxicillin			
	Amoxicillin Clavulanate			
Clinical Site	Children's Hospital of Philadelphia			
	Children's Hospital of Pittsburgh			
	Cincinnati Children's Hospital			
	Duke University			
	Vanderbilt University			

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR

[Programming Note: Rows will be added for additional sites that enroll at least one subject, as needed.]

Table 48: As Treated Analysis of Association between Ordinal Clinical Response and the Number of Days of Antibiotic Use at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

Outcome Assessment Visit[1]	Proportional Odds[2] Odds Ratio for 1 Additional Day of Antibiotic Use	95% CI	P-value
#1	x.xx	(x.xx, x.xx)	x.xxx
#2	x.xx	(x.xx, x.xx)	x.xxx

[1] Analysis at Outcome Assessment Visit #1 uses the subset of the CC-V1 analysis population that did not receive systemic antibiotic unrelated to pneumonia on or prior to Day 5. Analysis at Outcome Assessment Visit #2 uses the subset of the CC-V2 analysis population that did not receive systemic antibiotic unrelated to pneumonia on or prior to Day 18.

[2] Odds ratio of an OCR at Outcome Assessment Visit #1 greater than k for the effect of one additional day of use of antibiotic, where k is any observed OCR value (1, 2, 3, …) besides the highest observed value.

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.1.1 Solicited Adverse Events

Table 49: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Treatment Group - Standard Course

Standard Course																																
Symptom	**Day 1 (N=X)**			**Day 2 (N=X)**			**Day 3 (N=X)**			**Day 4 (N=X)**			**Day 5 (N=X)**			**Day 6-9 (N=X)**			**Day 10-13 (N=X)**			**Day 14-18** (N=X)			**Day 19-25 (N=X)**			**Day 1-25 (N=X)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Irritability																														
Vomiting																														
Diarrhea																														
Allergic Reaction																														
Stomatitis																														
Candidiasis																														

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table with similar format:

Table 50: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Treatment Group – Short Course

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Standard Course

Symptom	Severity	Standard Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Irritability	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Vomiting	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Diarrhea	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Allergic Reaction	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Stomatitis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Standard Course *(continued)*

Symptom	Severity	Standard Course								
		Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
Candidiasis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table 52: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Short Course

Symptom	Severity	Short Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Irritability	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Vomiting	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Diarrhea	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Allergic Reaction	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Stomatitis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 52: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Short Course *(continued)*

Symptom	Severity	Short Course								
		Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
Candidiasis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table 53: Number and Percentage of Subjects Experiencing Solicited Adverse Events of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group

Symptom	Severity	Standard Course (N=X)		Short Course (N=X)		Odds Ratio (95% CI)	P-Value
		n (%)	95% CI	n (%)	95% CI		
Any Symptom	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Irritability	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Stomatitis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 54: Listing of Serious Adverse Events

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

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Laboratory Data Over Time

Not applicable

14.3.5 Displays of Laboratory Results

Not applicable

14.3.6 Displays of Vital Signs

Table 55: Summary of Vital Signs by Visit and Treatment Group

		Enrollment Visit		Outcome Assessment Visit #1		Outcome Assessment Visit #2	
		Standard Course	Control	Standard Course	Control	Standard Course	Control
Temperature (°F)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Respiratory Rate (breaths/min.)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Pulse (beats/min.)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx

14.4 Summary of Concomitant Medications

Table 56: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

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

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

Table 57: Medically Attended Visits

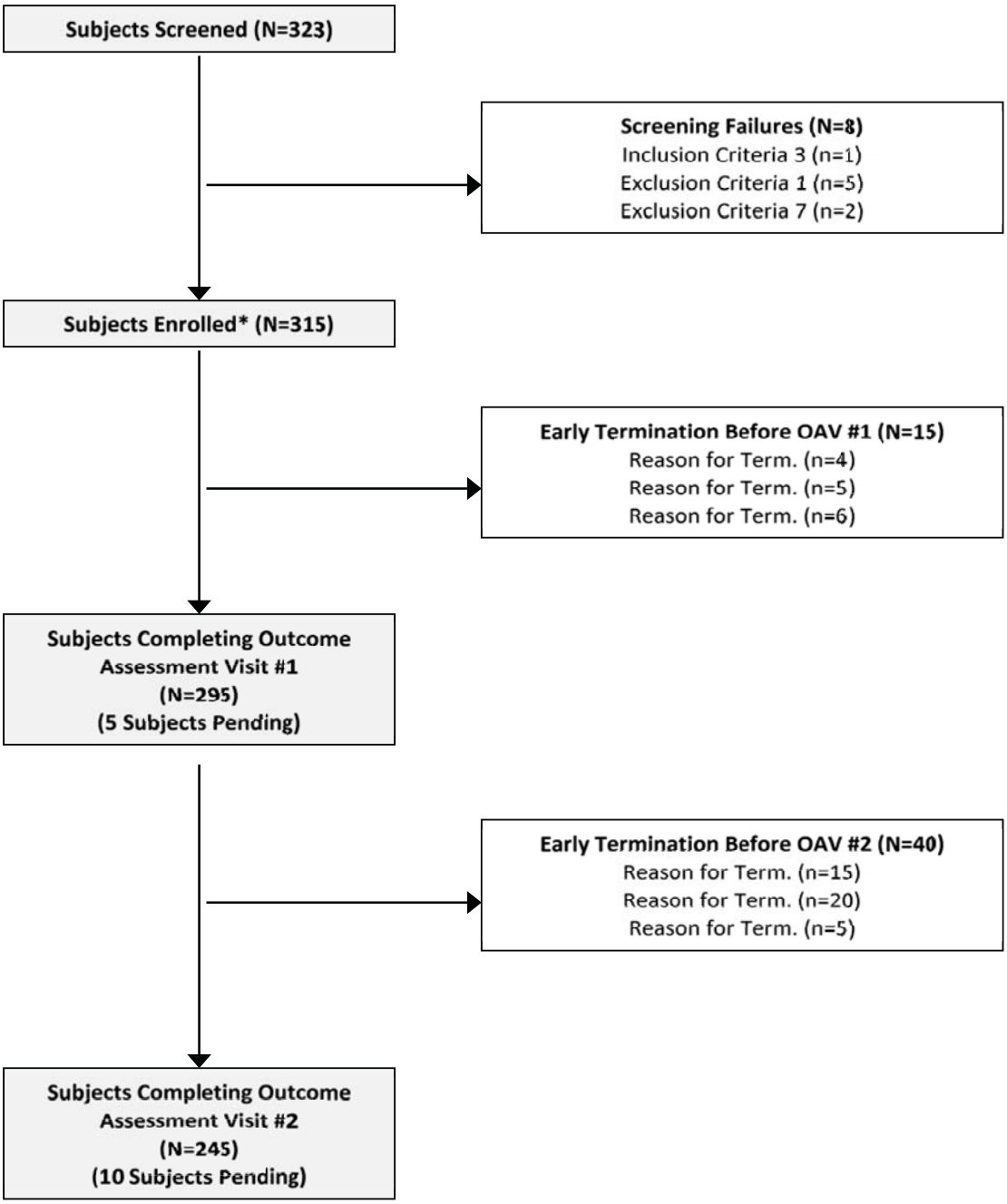
	Day 1-5		Day 6-18	
	Standard Course n (%) (N=X)	**Short Course n (%) (N=X)**	**Standard Course n (%) (N=X)**	**Short Course n (%) (N=X)**
Emergency Department Visit[1]				
Primary Care Provider Visit[1]				
Study Physician Visit[1]				
Urgent Care Visit[1]				
Other Medically Attended Visit[1]				
Additional Antibiotic Received[2]				
Drainage of pleural fluid[2]				
Placement of a chest tube[2]				
Video assisted thoracoscopic surgery[2]				
Thoracotomy procedure[2]				
Any other surgical procedure[2]				
Hospitalization[2]				

1 Visit associated with worsening study pneumonia.
2 For pneumonia or a complication of pneumonia.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

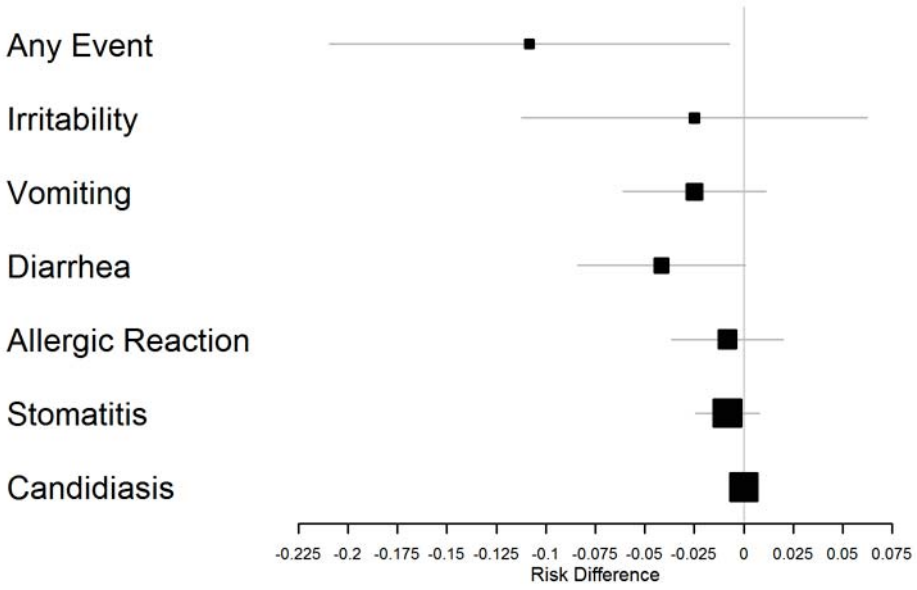
Figure 2: CONSORT Flow Diagram



*All enrolled subjects will be evaluable for the primary (ITT) analysis.

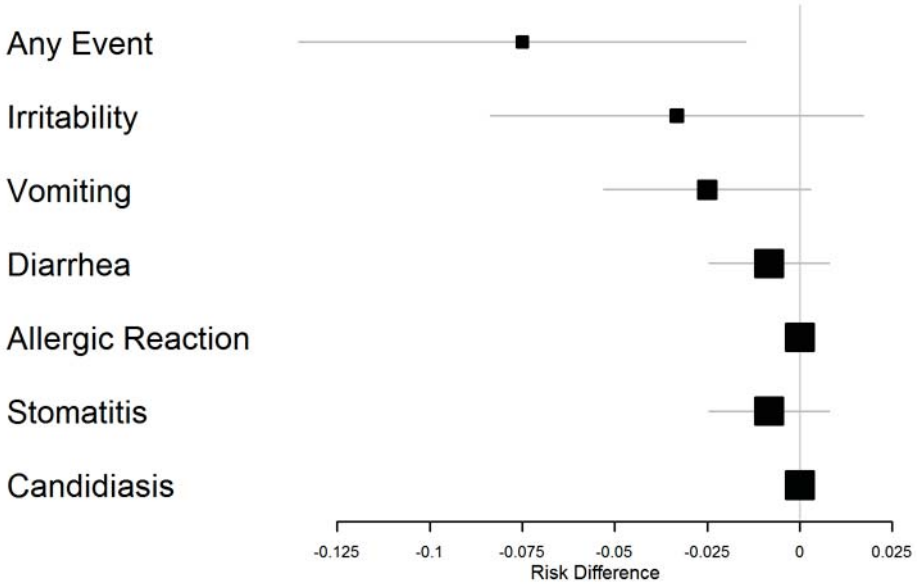
[Programming Note: Diagram will include breakdown by treatment arm and will add the 'Eligible but not Enrolled' category under subjects screened.]

Figure 3: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Mild, Moderate, or Severe - CC-V1 Population



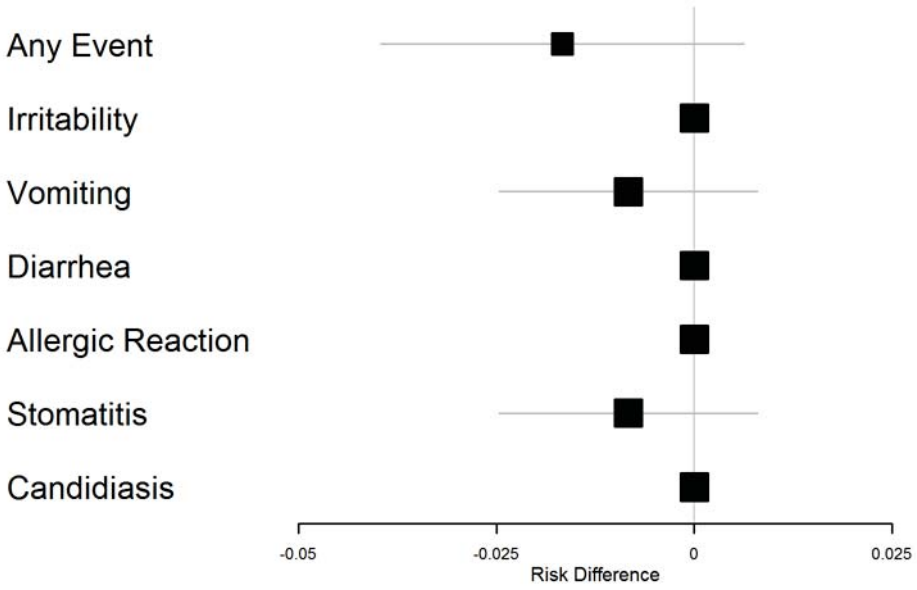
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 4: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Moderate or Severe - CC-V1 Population



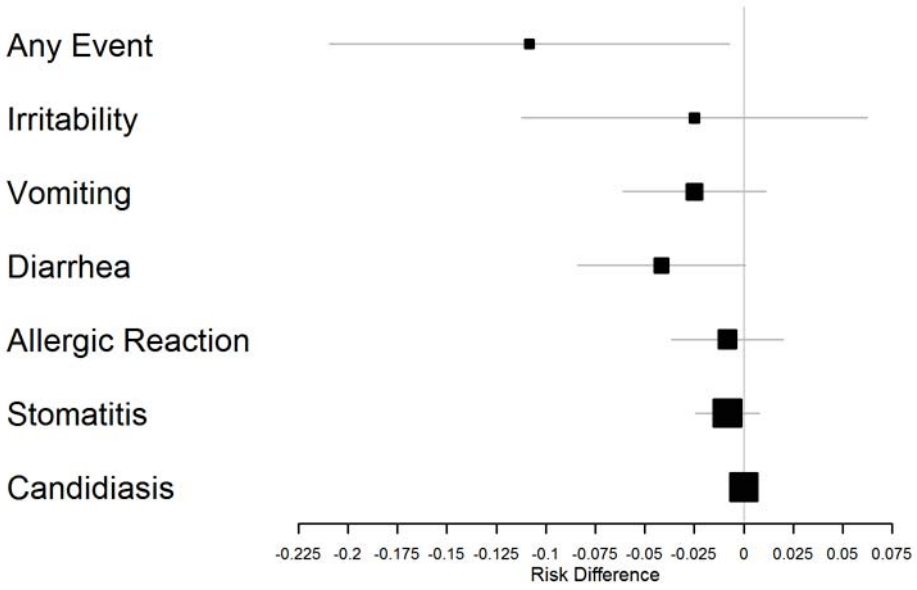
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 5: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Severe - CC-V1 Population



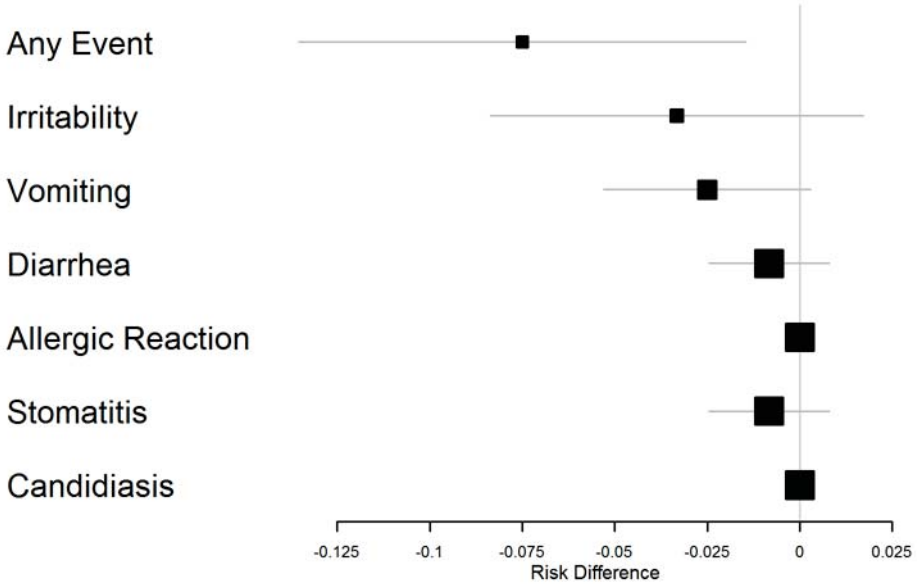
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 6: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Mild, Moderate, or Severe - CC-V2 Population



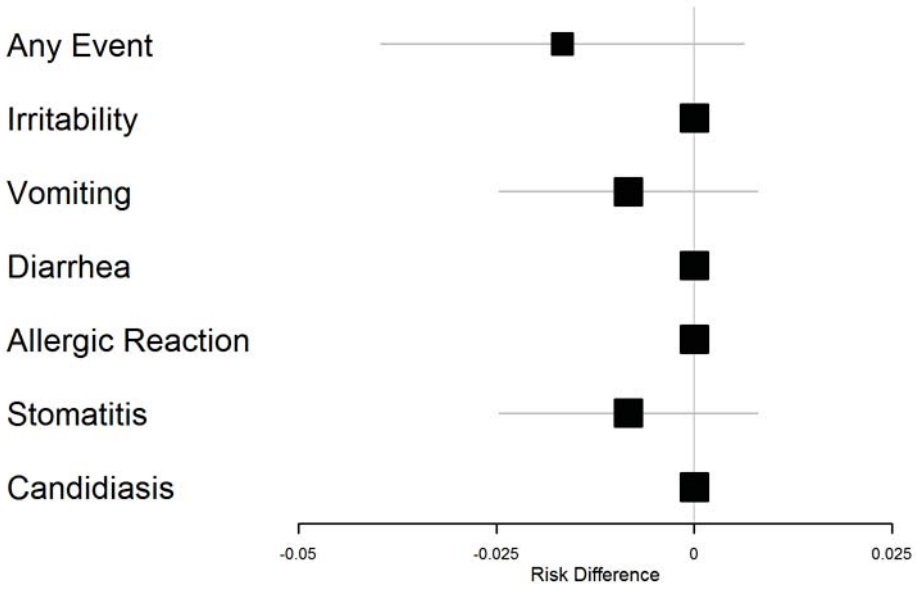
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 7: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Moderate or Severe - CC-V2 Population



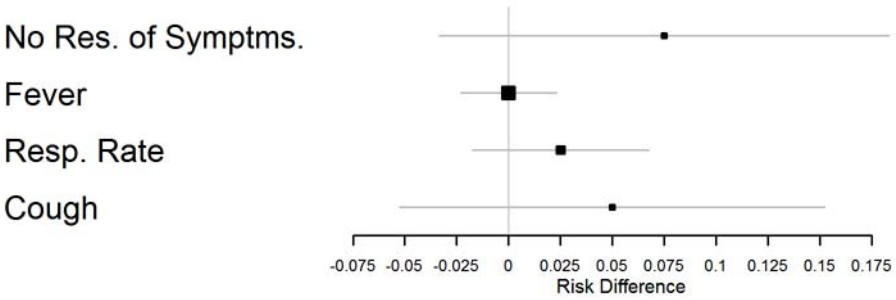
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 8: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Severe - CC-V2 Population



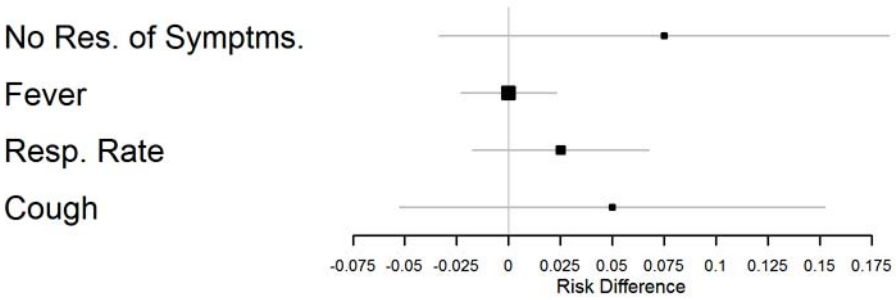
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 9: Forest Plot of Risk Difference of Lack of Resolution of Symptoms and Its Components - Outcome Assessment Visit #1 - CC-V1 Population



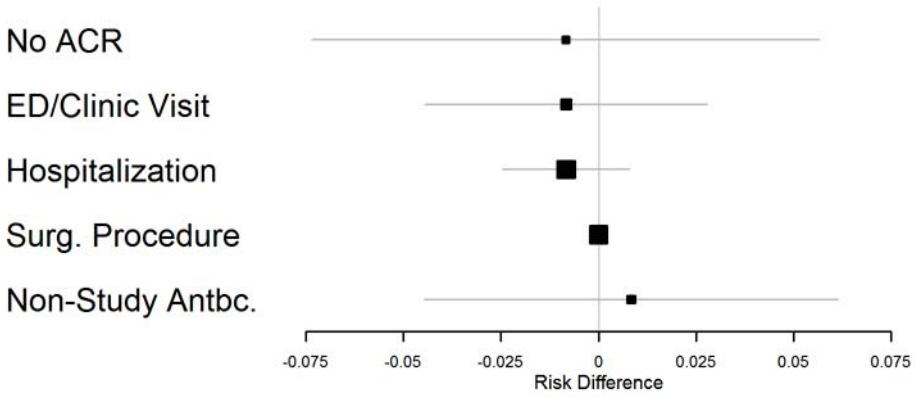
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 10: Forest Plot of Risk Difference of Lack of Resolution of Symptoms and Its Components - Outcome Assessment Visit #2 - CC-V2 Population



Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 11: Forest Plot of Risk Difference of Lack of Adequate Clinical Response and Its Components - Outcome Assessment Visit #1 - CC-V1 Population

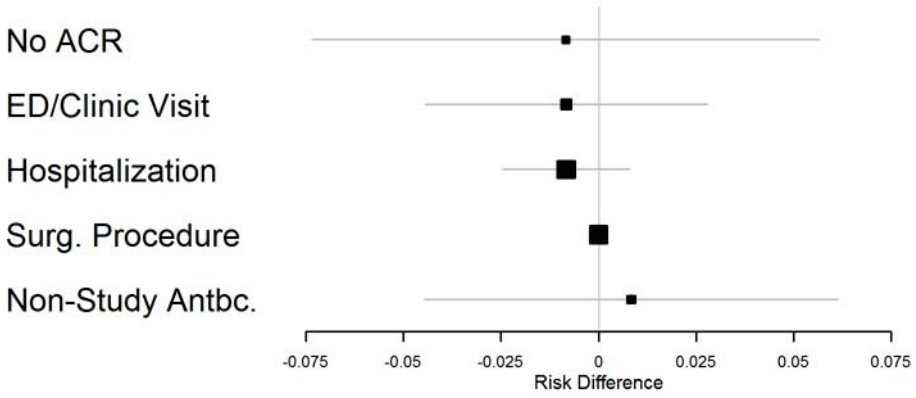


Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 12: Forest Plot of Risk Difference of Any Receipt of Non-Study Antibiotics or Medically Attended Visit - Outcome Assessment Visit #1 - CC-V1 Population

[Figure 12 will repeat Figure 11 without the No ACR confidence interval and will show confidence intervals for all events Day 1 – Day 5 (ED/Clinic Visit, Hospitalization, Surgical Procedure, and receipt of Non-Study Antibiotic) rather than only those satisfying the definition for lack of adequate clinical response.]

Figure 13: Forest Plot of Risk Difference of Lack of Adequate Clinical Response and Its Components - Outcome Assessment Visit #2 - CC-V2 Population

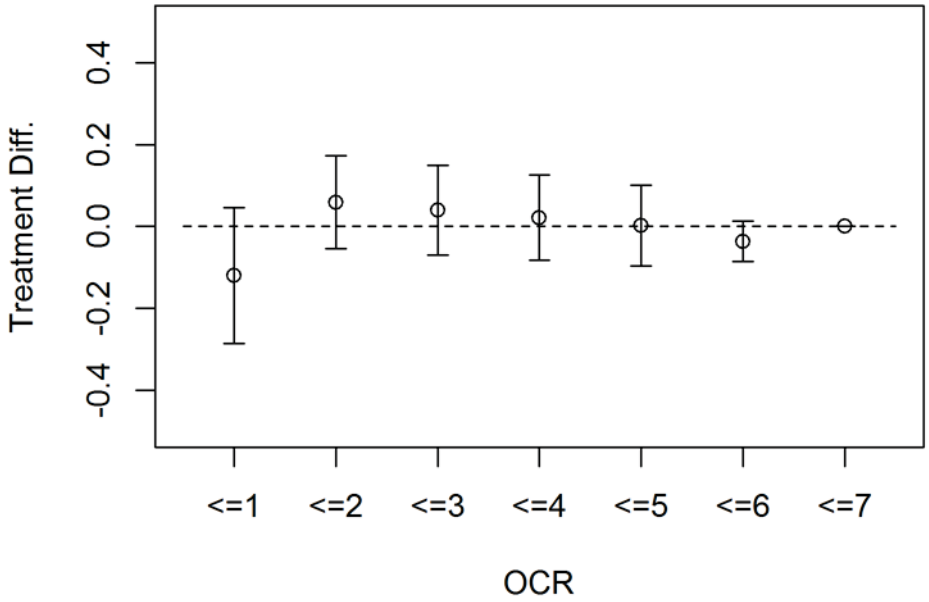


Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 14: Forest Plot of Risk Difference of Any Receipt of Non-Study Antibiotics or Medically Attended Visit - Outcome Assessment Visit #2 - CC-V2 Population

[Figure 14 will repeat Figure 13 without the No ACR confidence interval and will show confidence intervals for all events Day 1 – Day 18 (ED/Clinic Visit, Hospitalization, Surgical Procedure, and receipt of Non-Study Antibiotic) rather than only those satisfying the definition for lack of adequate clinical response.]

Figure 15: 95% Cumulative Difference Plot[1] of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - ITT Analysis



[1] Plots the 95% confidence intervals of the difference in the probability Pr(OCR≤k | treatment=m), where k=1,2,3,4,5,6,7 and m=0,1, between the two treatment groups. Note there can be no difference in Pr(OCR≤8 | treatment=m) since the probability is always 1 for each treatment arm, so only the first seven levels of the OCR are plotted.

Figures with similar format:

Figure 16: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - CC-V1 Analysis

Figure 17: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - ATP-V1 Analysis

Figure 18: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - Worst Case Analysis

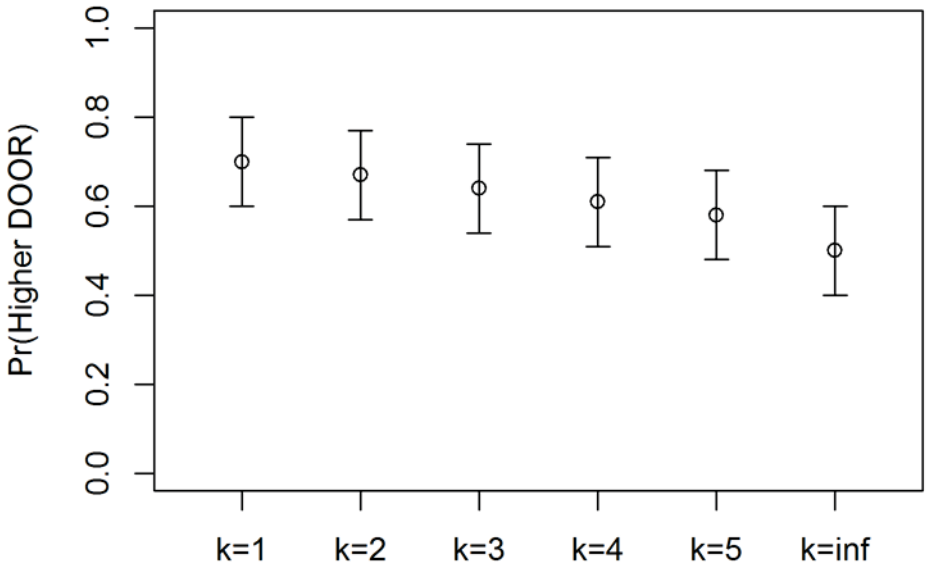
Figure 19: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - ITT Analysis

Figure 20: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - CC-V2 Analysis

Figure 21: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - ATP-V2 Analysis

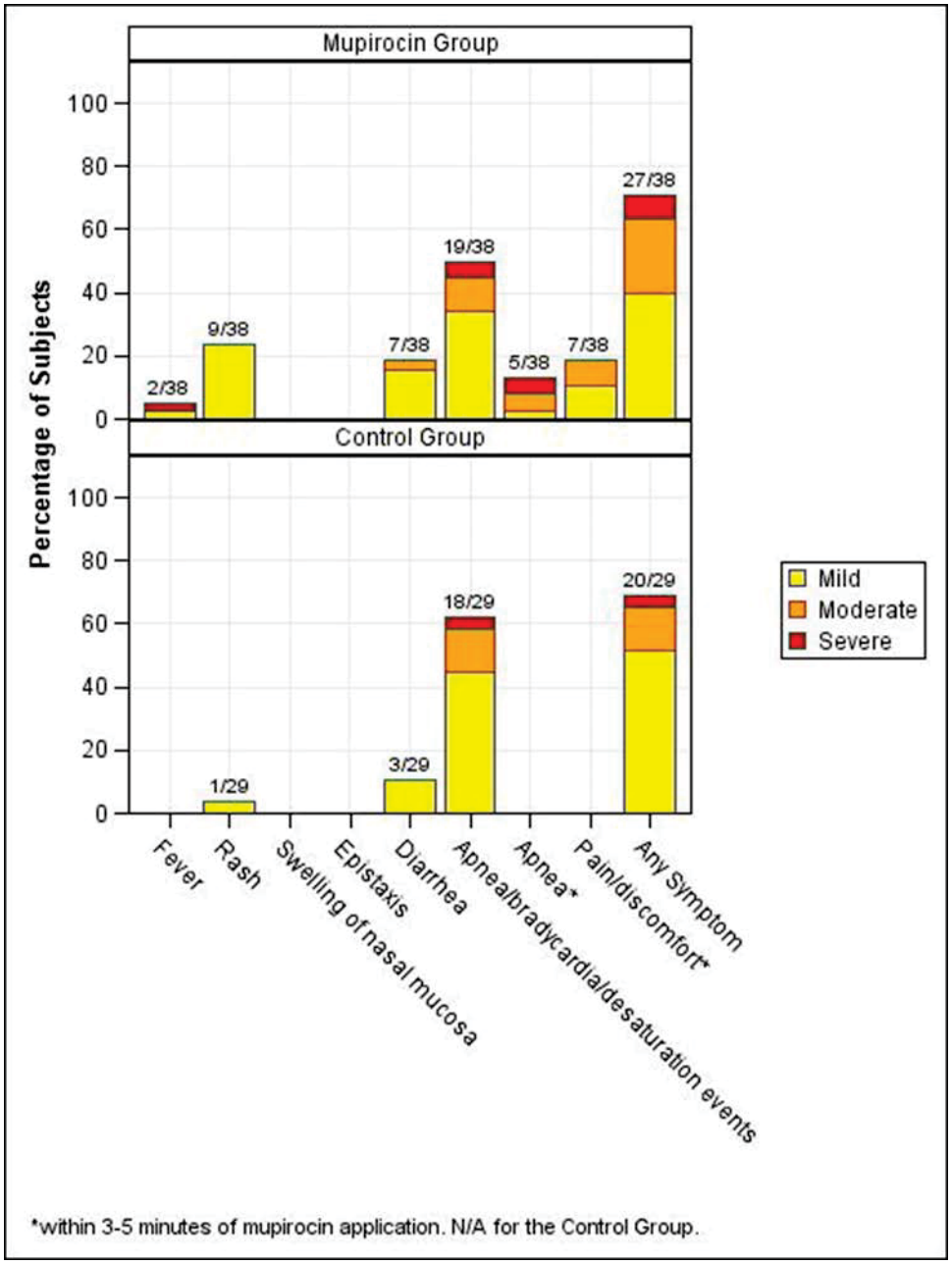
Figure 22: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - Worst Case Analysis

Figure 23: C-V1 Evaluation of DOOR at Outcome Assessment Visit #1 - Minimum Required Difference in Days for Antibiotic Use "Tie-Breaking" Varies k=1,2,3,4,5, or Infinity



14.3.1.1 Solicited Adverse Events

Figure 24: Maximum Severity of Solicited Adverse Events (by Symptom)



[Programming Note: This figure will present maximum severity of solicited events separately by treatment group. The mockup is an example only. The actual figure will contain treatment groups and solicited events relevant to the 14-0079 protocol.]

14.3.5 Displays of Laboratory Results

Not applicable

APPENDIX 3. LISTINGS MOCK-UPS

LIST OF LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

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

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 - Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1 - Subject-Specific Protocol Deviations

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

Listing 3: 16.2.2.2 - Non-Subject-Specific Protocol Deviations

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3 - Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., ITT, CC-V1, ATP-1]	[e.g., ITT, CC-V2, ATP-2]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

16.2.4 Demographic Data

Listing 5: 16.2.4.1 - Demographic Data

Treatment Group	Subject ID	Sex	Initial Antibiotic	Initial Site of Treatment	Age at Enrollment (months)	Ethnicity	Race

[Implementation Note: If a subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."]

Listing 6: 16.2.4.2 - Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

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

Listing 7: 16.2.5 - Treatment Compliance

Treatment Group	Subject ID	Dose(s) Missed	Extra Doses
		[1,2,3,4,5,6,7,8,9,10]	

16.2.6 Solicited Events

Listing 8: 16.2.6 - Solicited Events

Treatment Group	Subject ID	Study Day	Irritability	Vomiting	Diarrhea	Allergic Reaction	Stomatitis	Candidiasis

16.2.7 Serious Adverse Events

Listing 9: 16.2.7 - Serious Adverse Events

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

16.2.8 Vital Signs and Physical Exam Findings

Listing 10: 16.2.8.1 - Vital Signs

Treatment Group	Subject ID	Visit Number	Temperature (°F)	Respiration Rate (breaths/min)	Pulse (beats/min)

Listing 11: 16.2.8.2 - Physical Assessment Findings

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.9 Concomitant Medications

Listing 12: 16.2.9 - Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

16.2.10 Medically Attended Visits

Listing 13: 16.2.10.1 - Medically Attended Visits - Standard Course

Subject ID	Visit Study Day	Visit Type[1]	Antibiotic[1]	Surgery[1]	Hospitalization[1]	Hospital Admit Day	Hospital Discharge Day

[1]Asterisk indicates the visit, antibiotic, surgery, or hospitalization were due to pneumonia or a complication of pneumonia.

Listing 14: 16.2.10.2 - Medically Attended Visits - Short Course

Subject ID	Visit Study Day	Visit Type[1]	Antibiotic[1]	Surgery[1]	Hospitalization[1]	Hospital Admit Day	Hospital Discharge Day

[1]Asterisk indicates the visit, antibiotic, surgery, or hospitalization were due to pneumonia or a complication of pneumonia.

16.2.11 Cough

Listing 15: 16.2.11.1 - Cough - Standard Course

	Cough Severity by Study Day or Visit																										
Subject ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**OAV[1]#1**	**OAV[1]#2**	**ETV[2]**

[1] OAV = Outcome Assessment Visit
[2] ETV = Early Termination Visit

Listing 16: 16.2.11.2 - Cough - Short Course

	Cough Severity by Study Day or Visit																											
Subject ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**OAV[1]#1**	**OAV[1]#2**	**ETV[2]**

[1] OAV = Outcome Assessment Visit
[2] ETV = Early Termination Visit

16.2.12 Presence of Fever in Previous 24 Hours

Listing 17: 16.2.12.1 - Presence of Fever in Previous 24 Hours - Standard Course

Subject ID	Outcome Assessment Visit #1		Outcome Assessment Visit #2		Early Termination Visit	
	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]

[1] Recorded oral, rectal, axillary, or tympanic temperature ≧38.3˚C (100.9˚F)
[2] Fever attributed to a process unrelated to the prior diagnosis of pneumonia

[Programming Note: Listing programmed from ACRTEMP and ACRFEV only.]

Listing 18: 16.2.12.2 - Presence of Fever in Previous 24 Hours - Short Course

Subject ID	Outcome Assessment Visit #1		Outcome Assessment Visit #2		Early Termination Visit	
	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]

[1] Recorded oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F)
[2] Fever attributed to a process unrelated to the prior diagnosis of pneumonia

16.2.13 Ordinal Clinical Response and DOOR, According to CC-V1 and CC-V2 Analyses[1]

Listing 19: 16.2.13 - Ordinal Clinical Response and DOOR, According to CC-V1 and CC-V2 Analyses[1]

Subject ID	Treatment Group	Outcome Assessment Visit #1			Outcome Assessment Visit #2		
		Ordinal Clinical Response	Days of Antibiotic Use	DOOR	Ordinal Clinical Response	Days of Antibiotic Use	DOOR

[1] Ordinal Clinical Response, Days of Antibiotic Use, and DOOR at Outcome Assessment Visits #1 and #2 are only listed for subjects that had the respective Outcome Assessment Visit (no imputed values are shown).

APPENDIX 4. NCA TEMPLATE

See separate document, if applicable.

DMID 14-0079 SAP Version 1.0, 11MAY2018
Updated in
DMID 14-0079 SAP Version 2.0, 24FEB2020

SAP:
Note: Page numbers refer to final SAP document not in track changes view.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for Change
1	Page 16, Sec 6.2, Timing of Analysis	The final analysis will be performed after database lock.	The final analysis will be performed after database lock. Specific tables and figures may be released after DMID approval prior to CSR completion.	To allow early release of tables and figures for abstract preparation for ID week
2	Page 16, Sec 6.3, Analysis Populations		ITT Exclusions • Subject became ineligible before taking study product.	To exclude those subjects who became ineligible before Day 1 if they didn't take any study product

DMID 14-0079 SAP Version 1.0, 11MAY2018
Updated in
DMID 14-0079 SAP Version 2.0, 24FEB2020

SAP:
Note: Page numbers refer to final SAP document not in track changes view.

3	Page 16, Sec 6.3, Analysis Populations	ATP-V1 Exclusion Reasons • The subject was excluded from CC-V1 cohort • Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5 • Not excluded for any reason above, major protocol deviation (see Section 6.3.3; subjects will be tabulated by type of protocol deviation) ATP-V2 Exclusion Reasons • The subject was excluded from CC-V2 cohort • Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5 • Not excluded for any reason above, major protocol deviation (see Section 6.3.3, subjects will be tabulated by type of protocol deviation)	ATP-V1 Exclusion Reasons • The subject was excluded from CC-V1 cohort • Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5 • Not excluded for any reason above, major protocol deviation (see Section 6.3.3; subjects will be tabulated by type of protocol deviation) • Outcome Assessment Visit #1 occurred out of the protocol defined window of Day 6-10 • Outcome Assessment Visit #1 did not occur as an in-person visit ATP-V2 Exclusion Reasons • The subject was excluded from CC-V2 cohort • Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5 • Not excluded for any reason above, major protocol deviation (see Section 6.3.3, subjects will be tabulated by type of protocol deviation) • Outcome Assessment Visit #2 occurred out of the protocol defined window of Day 19-25	To add protocol deviations determined by the study team

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DMID 14-0079 SAP Version 2.0, 24FEB2020

SAP:
Note: Page numbers refer to final SAP document not in track changes view.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for Change
			• Outcome Assessment Visit #2 did not occur as an in-person visit	
4	Page 17-18, Sec 6.3.1, Intention-to-Treat (ITT) Cohort	The ITT cohort will include all randomized subjects. The analyses on the ITT cohort will be performed per randomized treatment assignment. Subjects randomized but not treated will be analyzed in the ITT cohort, but will have adequate clinical response and its components treated as missing.	The ITT cohort will include all randomized subjects that were still eligible on Day 1 of the study. The analyses on the ITT cohort will be performed per randomized treatment assignment. Randomized subjects who became ineligible before Day 1 of the study and did not take any study product will be excluded from ITT. Subjects randomized but not treated for other reasons other than ineligibility will be analyzed in the ITT cohort, but will have adequate clinical response and its components treated as missing.	Add more details about the new definition of ITT to exclude subjects who became ineligible before the Day 1 date
5	Page 22, Sec 6.5.3, Resolution of Symptoms at OAV#1 or OAV#2	Otherwise, if fever, respiratory rate, and presence of cough are all non-missing at OAV#1 or OAV#2, then the subject has resolution of symptoms at the respective Outcome Assessment Visit	Otherwise, if fever, respiratory rate, and presence of cough are all non-missing and are indicated as 'No' at OAV#1 or OAV#2, then the subject has resolution of symptoms at the respective Outcome Assessment Visit.	To clarify the definition of Resolution of symptoms

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SAP:
Note: Page numbers refer to final SAP document not in track changes view.

6	Page 22, Sec 6.5.4, Most Severe Solicited Event at OAV#1 and OAV#2	If a subject had severity grades (0 to 3) recorded for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 5, inclusive, then the most severe solicited event at OAV#1 will be the maximum severity grade taken across all solicited events from Day 1 to Day 5. If a subject had any solicited event of severity grade 3 from Day 1 to Day 5, then the most severe solicited event at OAV#1 will be grade 3, regardless of the presence of missing data during that period. Otherwise, if a subject has missing data for the severity grade of any solicited event from Day 1 to Day 5 then most severe solicited event at OAV#1 will be missing. If a subject had severity grades (0 to 3) recorded for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 18, inclusive, then the most severe solicited event at OAV#2 will be the maximum severity grade taken across all solicited events from Day 1 to Day 18. If a subject had any solicited event of severity grade 3 from Day 1 to Day 18, then the most severe solicited event at OAV#2 will be grade 3, regardless of the presence of missing data during that period. Otherwise, if a subject has missing data for the severity grade of any solicited event from Day 1 to Day 18 then most	The maximum severity at OAV #1 will be calculated based on the following rules: • If a subject has missing data for the severity grade of any solicited event for two consecutive days or has missing data for more than two days from Day 1 to Day 5 then the most severe solicited event at OAV#1 will be missing. • Otherwise if a subject has missing data for one or two non-consecutive days from Day 1 to Day 5 then the missing severity will be imputed as the maximum severity grade taken across the previous day and the day after the day with a missing severity. As a special case, for subjects missing severity for Day 1, the missing severity will be imputed as the Severity from Day 2. For subjects missing severity at Day 5 but not missing severity at Day 6, the missing severity will be imputed as the maximum of severity gradings from Day 4 and Day 6. For these subjects with severity grades (0 to 3) recorded or imputed for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 5, inclusive, the most severe solicited event at OAV#1 will be the maximum severity grade	To expand the number of subjects in CC-V1, CC-V2 if they are only missing very few days of solicited symptoms only

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Note: Page numbers refer to final SAP document not in track changes view.

		severe solicited event at OAV#2 will be missing.	taken across all solicited events from Day 1 to Day 5. • If a subject had any solicited event of severity grade 3 from Day 1 to Day 5, then the most severe solicited event at OAV#1 will be grade 3, regardless of the presence of missing data during that period. In a similar manner, the maximum severity at OAV #2 will be calculated based on the following rules: • If a subject has missing data for the severity grade of any solicited event for more than three consecutive days or has missing data for more than five days from Day 1 to Day 18 then the most severe solicited event at OAV#2 will be missing. • Otherwise if a subject has missing data for five days or less and no more than three of them are consecutive Day 1 to Day 18 then the missing severity will be imputed as the maximum severity grade taken across the previous day and the day after the day with a missing severity. As a special case, for subjects missing severity for Day 1, the missing severity will be imputed as the Severity from Day 2. For subjects missing severity at Day 18, the missing severity will be imputed as the severity from Day 17. For these subjects with severity grades	

SAP:
Note: Page numbers refer to final SAP document not in track changes view.

#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for Change
			(0 to 3) recorded or imputed for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 18, inclusive, the most severe solicited event at OAV#2 will be the maximum severity grade taken across all solicited events from Day 1 to Day 18. • If a subject had any solicited event of severity grade 3 from Day 1 to Day 18, then the most severe solicited event at OAV#2 will be grade 3, regardless of the presence of missing data during that period.	

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SAP:
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7	Page 40, Sec 8.4.1, Multiple Imputation of Missing Ordinal Clinical Response and DOOR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2	Severity of cough on Day 1 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 1 (0, 1, 2, or 3) • Severity of cough on Day 2 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 2 (0, 1, 2, or 3) • Severity of cough on Day 3 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 3 (0, 1, 2, or 3) • Severity of cough on Day 4 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 4 (0, 1, 2, or 3) • Severity of cough on Day 5 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 5 (0, 1, 2, or 3)	• Severity of cough on Day 1 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 1(0, 1, 2, or 3) o Note: Some missing values for Day 1 will first be imputed as described in Section 6.5.4 • Severity of cough on Day 2 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 2 (0, 1, 2, or 3) o Note: Some missing values for Day 2 will first be imputed as described in Section 6.5.4 • Severity of cough on Day 3 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 3 (0, 1, 2, or 3) o Note: Some missing values for Day 3 will be first imputed as described in Section 6.5.4 • Severity of cough on Day 4 as recorded on Solicited Events form (0, 1, 2, or 3)	To add clarification on how missing daily maximum severity might be imputed in some cases

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#	Page and Section	Originally in Version 1.0	Updated in Version 2.0	Rationale for Change
			• Severity of most severe solicited event (besides cough) on Day 4 (0, 1, 2, or 3) o Note: Some missing values for Day 4 will first be imputed as described in Section 6.5.4 • Severity of cough on Day 5 as recorded on Solicited Events form (0, 1, 2, or 3) • Severity of most severe solicited event (besides cough) on Day 5 (0, 1, 2, or 3) ~~o~~ Note: Some missing values for Day 5 will first be imputed as described in Section 6.5.4	
8	Page 60, Analysis Populations by Treatment Group		-Updated the table with new definitions for ITT, ATP-V1, ATP-V2	To be consistent with the new definition of ATP-V1, ATP-V2
9	Page 104, Table 49, Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Treatment Group	-Single table for both treatment groups	-Created separate tables, Table 49 for the standard course and Table 50 the other for the short course. -The rest of the table number were shifted accordingly	To avoid very wide tables. Given the big number of timepoints, the original table was not going to fit on a page

CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
ADDENDUM A
for
DMID Protocol: 14-0079

EXPLORATORY METAGENOMICS ANALYSIS

Study Title:

A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP)

NCT02891915

Version 1.0

DATE: 05FEB2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ARG	Antibiotic Resistance Genes
ATP	According to Protocol
CAP	Community Acquired Pneumonia
OAP	Online Analysis Pipeline
SAP	Statistical Analysis Plan
SARG	Structured Antibiotic Resistance Genes
ITT	Intention to Treat

SYNOPSIS

This Statistical Analysis Plan (SAP) Addendum to the main 14-0079 SAP describes planned analyses for the exploratory metagenomics endpoint of resistance genes per prokaryotic cell in throat samples from children collected at Visit 03 (Study Day 19-25). The goal is to compare the number of total resistance genes as well as beta-lactamase resistance genes per prokaryotic cell in throat swab samples from children receiving short course (5 days) vs. standard course (10 days) antibiotic therapy for Community Acquired Pneumonia (CAP). The hypothesis is that the distribution of the number of resistance genes will be different, specifically that children randomized to the short course (5 days) therapy arm will have fewer resistance genes detected.

1. ANALYSIS POPULATIONS

The analysis populations for the exploratory metagenomics endpoint analyses will be based on Intent-to-Treat (ITT) and According-to-Protocol (ATP) analysis populations as defined in the main SAP.

2. SAMPLE SIZE CONSIDERATIONS

Preliminary data on antibiotic resistance genes from 57 throat samples from the STAR study were used for the sample size calculation. The resistance gene data were blinded to treatment group assignment. Data regarding the distribution of 1) beta-lactamase genes and 2) total antibiotic resistance genes were divided into six equal intervals with an additional open interval on the right (i.e., seven intervals in total). Next, the percentage of participants in the treatment-pooled samples from both treatment groups falling in each interval was calculated. We used the observed percentages for the pooled data in each interval and assumed a 4% shift from each of the three intervals on the left to each of the three intervals on the right of the distribution between short course and standard course groups. This was achieved by adding 2% to the lower three categories and subtracting 2% for the highest three categories from the pooled estimate for the short course estimate and subtracting 2% to the lower three categories and adding 2% for the highest three categories from the pooled estimate for the standard course estimate. The resulting percentages of beta-lactamase genes in throat samples were (.07 .23 .30 .30 .09 .01 .00) in the short course group and (.03 .19 .26 .30 .13 .06 .03) in the standard course treatment group. The resulting percentages for the total resistance genes in throat sample were (.06 .21 .27 .35 .09 .02 .00) in the short course group and (.02 .17 .23 .35 .13 .07 .03) in the standard course treatment group. Assuming the following hypothesis:

- H_0: the distribution of the number of resistance genes per prokaryotic cell in the two arms (5 day and 10-day strategies) will be the same.
- H_1: the distribution of the number of resistance genes will be different, specifically that children randomized to the 5-day arm will have fewer resistance genes detected.

And a one-side alpha of 5%, these calculations suggest that a sample size of 200 total subjects (100 in each group) will achieve ~75% power to detect a difference between the two groups. As the actual difference in distribution may be larger than the assumed 12% of shift from the left side to the right side of the distribution, the estimate is considered conservative. Power curves are shown in Figure 1.

Figure 1: Power by Samples Size

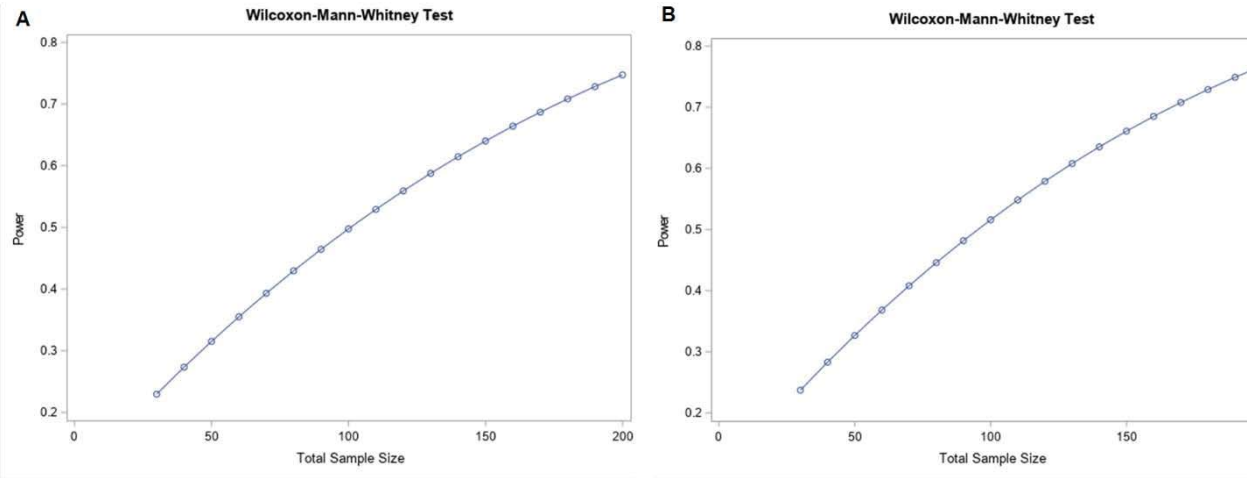


Figure 1 Power by samples size. A: Power to detect a difference between short course and standard course treatment: beta-lactamase genes in throat samples. B: Power to detect a difference between short course and standard course treatment: total antibiotic resistance genes in throat samples.

3. EXPLORATORY METAGENOMICS RESPONSE EVALUATIONS

3.1. Data Processing

Shotgun metagenomic sequence data will be generated from throat samples obtained at Visit 03 (Study Day 19-25). The antibiotic resistance genes (ARG) online analysis pipeline (OAP) v2.0 with the expanded structured antibiotic resistance genes (SARG) database will be used to classify and quantify antibiotic resistance genes [1]. The pipeline contains 12,307 reference sequences that encode 1,208 distinct resistance genes (referred to as ARG subtypes) and provides quantification of reads classified by resistance to each of 24 different antibiotics (type level). These include aminoglycoside, bacitracin, beta-lactam, bleomycin, albomycin, chloramphenicol, fosfomycin, fosmidomycin, fusaric-acid, fusidic-acid, kasugamycin, macrolide-lincosamide-streptogramin, multi-drug efflux pump, polymyxin, puromycin, quinolone, rifamycin, spectinomycin, sulfonamide, tetracenomycin C, tetracycline, trimethoprim, vancomycin, or unclassified. The output will include the total number of antibiotic resistance genes and the number of beta-lactamase resistance genes per prokaryote cell.

3.2. Data Summaries

Baseline characteristics by site and treatment group will be summarized based on ITT subjects for which metagenomics results were produced (Table 1, Table 2, Table 3, and Table 4). The minimum, Q1, median, Q3, and maximum number of genes by resistance to each of 24 different antibiotics and any antibiotic will be summarized by treatment group (5 days vs. 10 days), analysis population (ITT and ATP), clinical site, and antibiotic (amoxicillin, amoxicillin-clavulunate, cefdinir) (Table 5). In addition, boxplots that summarize the distribution for each antibiotic class as well as any antibiotic class will be contrasted between treatment groups, clinical site, and antibiotic for each analysis population. Individual data points will be overlaid on top of boxplots to represent both the data and boxplot summary statistics (Figure 2). In addition to boxplots, heatmaps that summarize the number of antibiotic resistance genes per prokaryotic cell will be generated for each analysis population (Figure 3). For better visualization, the data will be $\log_2$ transformed after adding a count of 0.5 to every observation. Euclidean distance in combination with complete linkage clustering will be utilized to generate subject and antibiotic class dendrograms. Different versions that color-code subjects by treatment (short vs. standard course), by clinical site, and antibiotic (amoxicillin, amoxicillin-clavulunate, cefdinir) will be provided.

3.3. Comparisons

For each analysis population, a one-sided Wilcoxon Rank Sum test will be carried out to assess statistically significant differences between the number of beta-lactamase resistance genes per prokaryotic cell as well as the total number of resistance genes per prokaryotic cell between treatment groups. Results will be presented as shown in Table 6. The randomization process is expected to control potential confounders such as sex and age which are thought to impact the microbiota and antibiotic resistome. For the subjects who contribute antibiotic resistance gene data in Visit 03 samples, the age categories (<24 Months vs. 24-71 Months), sex (males vs. females), and other important baseline characteristics will be compared between treatment groups using a Fisher's exact test (Table 7). If a strong imbalance between treatment groups is

observed for these variables, a negative binomial model that controls for these baseline covariates will be fitted and statistical significance of the difference in resistance gene numbers will be assessed using a likelihood ratio test.

4. REFERENCES

1. Yin, Xiaole, et al. "ARGs-OAP v2. 0 with an expanded SARG database and Hidden Markov Models for enhancement characterization and quantification of antibiotic resistance genes in environmental metagenomes." *Bioinformatics* 34.13 (2018): 2263-2270.

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 1: Summary of Categorical Demographic and Baseline Characteristics by Site

Demographic Category	Characteristic	Children's Hospital of Philadelphia (N=X)		Children's Hospital of Pittsburgh (N=X)		Cincinnati Children's Hospital (N=X)		Duke University (N=X)		Vanderbilt University (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Antibiotic	Amoxicillin	x	x	x	x	x	x	x	x	x	x	x	x
	Amoxicillin-Clavulunate	x	x	x	x	x	x	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x	x	x	x	x	x	x

[Programming Note: N=number of subjects for which microbiome results were obtained. Columns will be added for additional sites that enrolled at least one subject for which microbiome results were obtained, as needed.]

Table 2: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	Children's Hospital of Philadelphia (N=X)	Children's Hospital of Pittsburgh (N=X)	Cincinnati Children's Hospital (N=X)	Duke University (N=X)	Vanderbilt University (N=X)	All Subjects (N=X)
Age (Months)	Mean	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x

[Programming Note: N=number of subjects for which microbiome results were obtained. Columns will be added for additional sites that enrolled at least one subject for which microbiome results were obtained, as needed.]

Table 3: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group and Overall

Demographic Category	Characteristic	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x
	Female	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Antibiotic	Amoxicillin	x	x	x	x	x	x
	Amoxicillin-Clavulunate	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x
Clinical Trial Site	Children's Hospital of Philadelphia	x	x	x	x	x	x
	Children's Hospital of Pittsburgh	x	x	x	x	x	x
	Cincinnati Children's Hospital	x	x	x	x	x	x
	Duke University	x	x	x	x	x	x
	Vanderbilt University	x	x	x	x	x	x

[Programming Note: N=number of subjects for which microbiome results were obtained. Rows will be added for additional sites that enrolled at least one subject for which microbiome results were obtained, as needed.]

Table 4: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group and Overall

Variable	Statistic	Short Course (N=X)	Standard Course (N=X)	All Subjects (N=X)
Age (units)	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

Table 5: Summary Statistics for the Number of Resistance Genes by Antibiotic Class and Treatment Group (ITT Population)

	Short Course (N=X)					Standard Course (N=X)				
Antibiotic Class	**min**	**Q1**	**median**	**Q3**	**max**	**min**	**Q1**	**median**	**Q3**	**max**
Any class										
Aminoglycoside										
Bacitracin										
Beta-lactam										
Bleomycin										
Carbomycin										
Chloramphenicol										
Fosfomycin										
Fosmidomycin										
Fusaric-acid										
Fusidic-acid										
Kasugamycin										
Macrolide-lincosamide-streptogramin										
Multi-drug efflux pump										
Polymyxin										
Puromycin										
Quinolone										
Rifamycin										
Spectinomycin										
Sulfonamide										
Tetracenomycin C										
Tetracycline										
Trimethoprim										
Vancomycin										
Unclassified										

[Programming Note: N=number of subjects for which microbiome results were obtained. Generate this table for each analysis population, site (Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Cincinnati Children's Hospital, Duke University, Vanderbilt University, etc.) and antibiotic (Amoxicillin, Amoxicillin-Clavulunate, Cefdinir).]

Table 6: Wilcoxon Rank-Sum Test Results by Analysis Population and Antibiotic Class

Analysis Population	Antibiotic Class	Median Number of Resistance Genes (Short Course) (N=X))	Median Number of Resistance Genes (Standard Course) (N=X))	Wilcoxon Statistic	P-value
ITT Analysis Population	Beta-lactamase resistance genes	x	x	x.xxx	x.xxx
ITT Analysis Population	Total resistance genes	x	x	x.xxx	x.xxx
ATP Analysis Population	Beta-lactamase resistance genes	x	x	x.xxx	x.xxx
ATP Analysis Population	Total resistance genes	x	x	x.xxx	x.xxx

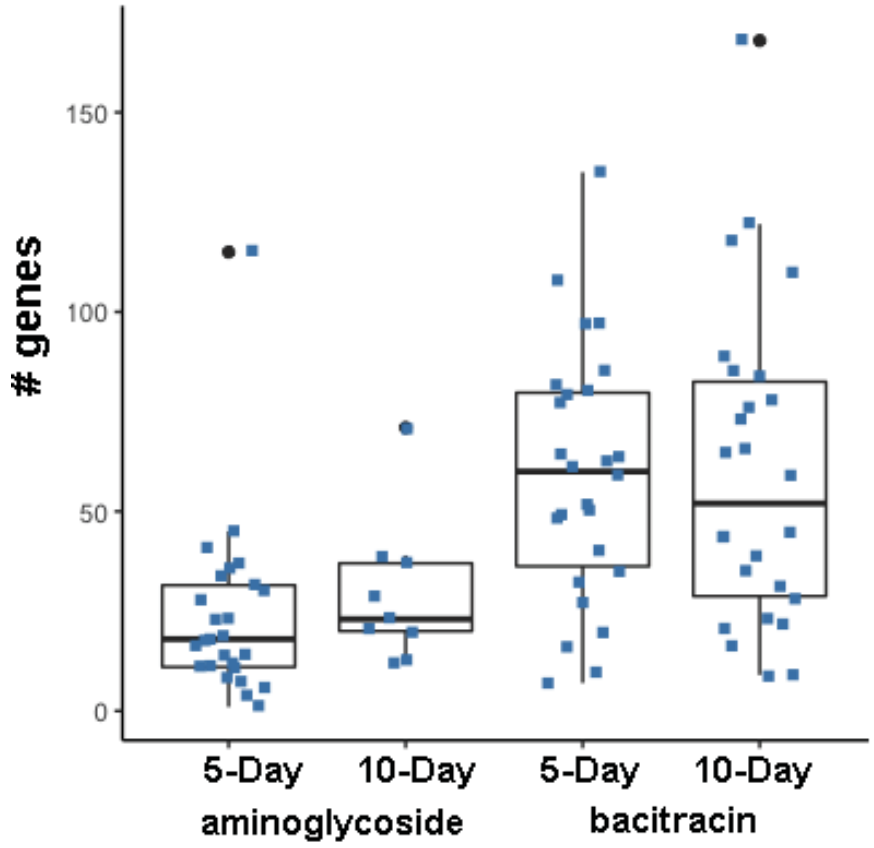
Table 7: Comparison of Select Baseline Characteristics

Variable	Categories	Fisher's Exact P-value
Age Group	<24 Months	x.xxx
	24-71 Months	
Sex	Male	x.xxx
	Female	
	Male	
Antibiotic	Amoxicillin	x.xxx
	Amoxicillin-Clavulunate	
	Cefdinir	
Initial Site of Treatment	ED	x.xxx
	Out-Patient/Urgent Care	

APPENDIX 2. FIGURE MOCK-UPS

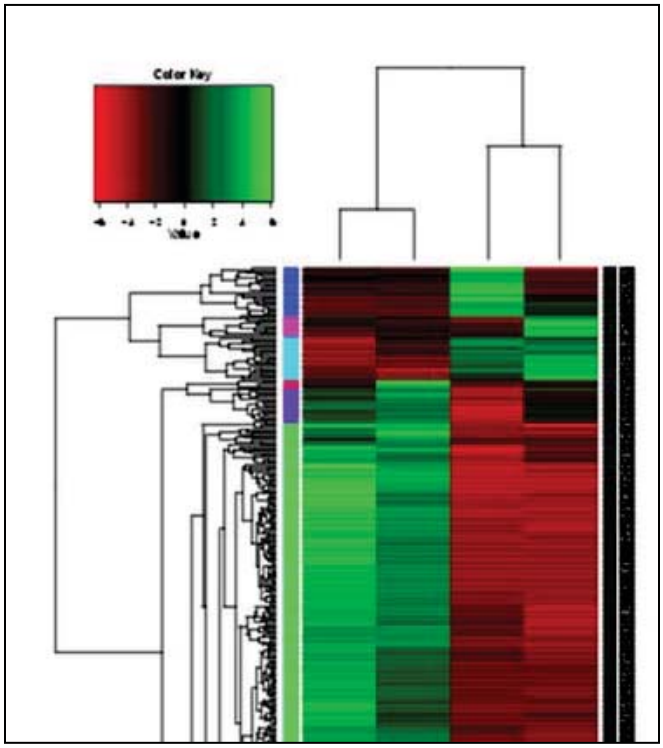
LIST OF FIGURES

Figure 2: Boxplot of the Number of Resistance Genes with Individual Observations by Antibiotic Class and Treatment Group (ITT Population)



[Programming Note: Generate boxplots for each antibiotic class as listed in Table 3. Repeat for the ATP population.
For each analysis population, generate a figure panel that includes this figure for each site (Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Cincinnati Children's Hospital, Duke University, Vanderbilt University, etc.) as well as a figure panels that includes this figure for each antibiotic (Amoxicillin, Amoxicillin-Clavulunate, Cefdinir).]

Figure 3: Heatmap of the Log_2 Number of Genes Per Prokaryotic Cell Per Across Antibiotic Classes (ITT Population)



[Programming Note: Rows will represent antibiotic classes as listed in Table 3 except for the "Any" class. Columns will represent subjects. Column and row dendrograms will be generated using complete linkage clustering in combination with the Euclidean distance. Repeat for the ATP population. Generate two versions of this figures for each population: one figure with subjects color-coded by site (Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Cincinnati Children's Hospital, Duke University, Vanderbilt University, etc.) and one version of the figure with subjects color-coded by antibiotic treatment (Amoxicillin, Amoxicillin-Clavulunate, Cefdinir).]