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

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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
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

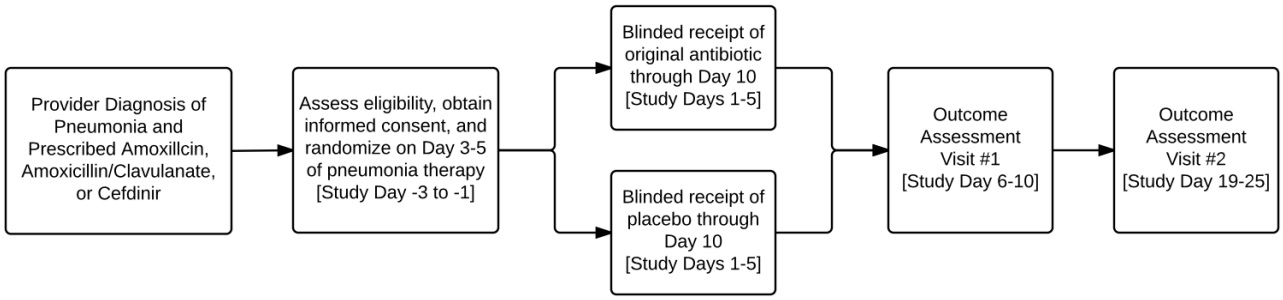
3. To compare the clinical response (a component of DOOR) among children 6-71 months of age with CAP assigned to a strategy of short course (5 days) vs standard course (10 days) outpatient beta-lactam therapy at Outcome Assessment Visits #1 and #2
4. To compare solicited events (a component of DOOR) 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



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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.