CLINICAL RESEARCH IN INFECTIOUS DISEASES

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

NCT02891915

Version 2.0

DATE: 24FEB2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 14-0079**
Development Phase:	Phase IV
Products:	Amoxicillin, amoxicillin-clavulanate, cefdinir and matching placebos
Form/Route:	Oral suspensions
Indication Studied:	Community Acquired Pneumonia
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	04OCT2016
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	24FEB2020
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

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

LIST OF ABBREVIATIONS *(continued)*

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

LIST OF ABBREVIATIONS *(continued)*

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

1. PREFACE

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

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

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

2. INTRODUCTION

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

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

2.1. Purpose of the Analyses

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

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

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

3.1.2. Secondary Objectives

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

3.1.3. Exploratory Objectives

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

3.2. Endpoints

3.2.1. Primary Endpoints

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

3.2.2. Secondary Endpoints

Secondary outcome measures include:

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

3.2.3. Exploratory Endpoints

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

3.3. Study Definitions and Derived Variables

DOOR is defined as follows:

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

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

Table 1: Ordinal Outcome

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

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

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

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

Adequate Clinical Response: Day 1 – Day 5

Resolution of Symptoms:

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

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

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

Solicited Events: Day 1 – Day 5

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

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

Adequate Clinical Response: Day 1 – Day 18

Resolution of Symptoms:

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

Solicited Events: Day 1 – Day 18

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

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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

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

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

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

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

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

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

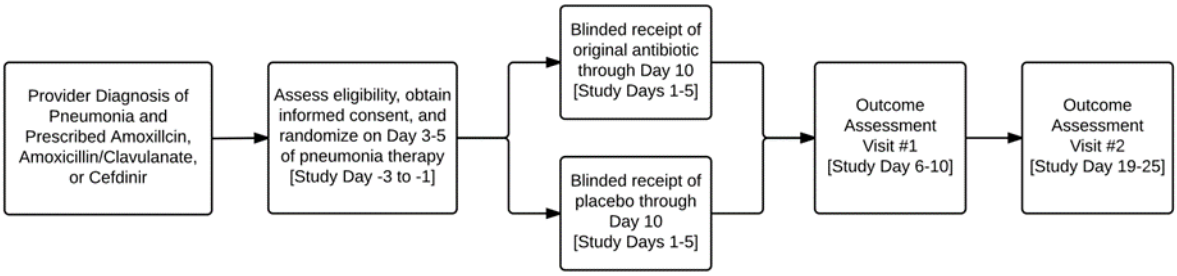
Visit 2: Outcome Assessment Visit #1, Day 6 to 10 (1-5 days after completing the study agent). Subjects will be evaluated for the components of the composite overall outcome, which include the adequacy of the subject's clinical response; persistence of symptoms of fever, tachypnea, or cough; the occurrence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

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

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

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

Figure 1: Schematic of the Study Design



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

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

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

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

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

4.3. Selection of Study Population

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

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

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

4.3.1. Inclusion Criteria

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

4.3.2. Exclusion Criteria

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

4.3.3. Reasons for Withdrawal

Subject Withdrawal

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

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

- Withdrawal of consent
- Subject lost to follow-up
- Termination of the study
- Any new information becomes available that makes further participation unsafe.

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

Discontinuation of Treatment

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

4.4. Treatments

4.4.1. Treatments Administered

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

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

Per International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at each participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded on screening logs maintained by each site.

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

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

system. A designated individual at each site will be provided with a treatment key, which links the treatment code to the actual treatment assignment, which will be kept in a secure place.

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

4.4.3. Blinding

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

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

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

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

4.5. Study Variables

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

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

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

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

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

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

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

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

All SAEs will be:

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

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

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

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

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

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

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

5. SAMPLE SIZE CONSIDERATIONS

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

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

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

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

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

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

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

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

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

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

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

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

6.2. Timing of Analyses

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

The final analysis will be performed after database lock. Specific tables and figures may be released after DMID approval prior to CSR completion.

6.3. Analysis Populations

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

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

ITT Exclusions

- Subject became ineligible before taking study product.

CC-V1 Exclusions

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

- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Solicited Event Severity Days 1-5
- Not excluded for any reason above, missing DOOR at Outcome Assessment Visit #1 component: Number of Days of Antibiotic Use

CC-V2 Exclusions

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

ATP-V1 Exclusion Reasons

- The subject was excluded from CC-V1 cohort
- Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5
- Not excluded for any reason above, major protocol deviation (see Section 6.3.3; subjects will be tabulated by type of protocol deviation)
- Outcome Assessment Visit #1 occurred out of the protocol defined window of Day 6-10
- Outcome Assessment Visit #1 did not occur as an in-person visit

ATP-V2 Exclusion Reasons

- The subject was excluded from CC-V2 cohort
- Not excluded for any reason above, subject did not receive at least one dose of study product each day from Day 1 to Day 5
- Not excluded for any reason above, major protocol deviation (see Section 6.3.3, subjects will be tabulated by type of protocol deviation)
- Outcome Assessment Visit #2 occurred out of the protocol defined window of Day 19-25
- Outcome Assessment Visit #2 did not occur as an in-person visit

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

The ITT cohort will include all randomized subjects that were still eligible on Day 1 of the study. The analyses on the ITT cohort will be performed per randomized treatment assignment.

Randomized subjects who became ineligible before Day 1 of the study and did not take any study product will be excluded from ITT. Subjects randomized but not treated for other reasons other than ineligibility will be analyzed in the ITT cohort, but will have adequate clinical response and its components treated as missing. Therefore, in ITT analyses, OCR and DOOR will be missing and will need to be imputed for subjects that were not treated. If data (solicited events, cough, etc.) are collected post-randomization for a subject that was not treated, that data will be used in the ITT analysis to assist in imputing the OCR and DOOR.

6.3.2. Complete Case (CC) Cohorts

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

6.3.3. According-to-Protocol (ATP) Cohorts

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

6.3.4. Safety Analysis Population

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

6.4. Covariates and Subgroups

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

6.5. Missing Data

While all efforts will be made to minimize missing data, some missing data is expected. Whenever possible, subjects terminating from the study early will be given an early termination visit during which the available components of the DOOR and related measures can be recorded. The primary analysis will use multiple imputation with linear models to impute values using available information (treatment, randomization strata variables, and available visit information), assuming a missing at random (MAR) model. Secondary analyses will further examine the robustness of this analysis, including a “worst case analysis” in which all imputations of missing

data will be the worst case (result in the lowest possible DOOR given available information) for subjects in the 5-day arm and best case for subjects in the 10-day arm. Day 1 in this study is defined as the date of first receipt of study product. If a subject has no record of study product administration or did not receive a first dose of study product, but has other post-randomization data, Day 1 will be imputed as the date 5 days after the date of first receipt of initial antibiotic.

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

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

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

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

Several variables are used to define the Adequate Clinical Response:

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

If a subject has OAV#1 and did not have a medically attended visit (MAV) from Day 1 to Day 5, inclusive, then the subject had adequate clinical response for OAV#1. If the subject had a MAV from Day 1 to Day 5 for which MAVABRX and MAVABCP were both YES (receipt of a non-

study systemic antibiotic for pneumonia), or for which MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were YES (treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures), then the subject did not have adequate clinical response at OAV#1. If the subject had a MAV from Day 1 to Day 5 for which MAVHOSP and MAVHPPN were both YES (subject was hospitalized for the treatment of pneumonia or pneumonia complications), then the subject did not have adequate clinical response at OAV#1. Otherwise, if the subject had a MAV from Day 1 to Day 5 and either MAVABRX was missing, MAVABRX was YES and MAVABCP was missing, or any of MAVPLEUR, MAVCHTB, MAVVIDEO, MAVTHOR, or MAVSURG were missing, then adequate clinical response at OAV#1 is missing. Otherwise, if a subject has one or more MAVs from Day 1 to Day 5, with no MAV indicating receipt of a non-study systemic antibiotic for pneumonia or treatment for a complication of pneumonia, including drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures and no hospitalization for treatment of pneumonia or pneumonia complications and no MAV missing data as described, then the subject has adequate clinical response at OAV#1. Note that for determining whether the medical treatment or hospitalization falls within the period of Day 1 to Day 5, the date of the initial MAV will be used (MAVVISDT), rather than specific dates of surgery or hospitalization entered on the MAV form.

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

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

```
if no recorded receipt of study product then ACR_OAV1=missing
else if death then ACR_OAV1=NO
```

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

then ACR_OAV1=missing
else ACR_OAV1=YES
```

6.5.2. Fever at OAV#1 or OAV#2

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

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

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

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

- If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is indicated as unrelated to prior diagnoses of pneumonia (ACRFEV), then fever at the OAV is absent
- If subject had a recorded temperature ≥ 38.3 °C (100.9 °F) (ACRTEMP) and fever is indicated as relatedness to prior diagnoses of pneumonia (ACRFEV) is missing, then fever at the OAV is missing
- If subject had a recorded temperature < 38.3 °C (100.9 °F) (ACRTEMP), then fever at the OAV is absent

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

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

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

If the subject died at any point of participation in the study, then the subject will be analyzed as not having resolution of symptoms at either Outcome Assessment Visit. Otherwise, if the subject did not have adequate clinical response at OAV#1 or OAV#2, then the subject will be analyzed as not having resolution of symptoms at the respective Outcome Assessment Visit(s). Otherwise, if fever, elevated respiratory rate, or presence of grade 2 or 3 cough is indicated at OAV#1 or OAV#2, then the subject does not have resolution of symptoms at the respective Outcome Assessment Visit (regardless of whether some components of the resolution of symptoms are missing). Otherwise, if fever, respiratory rate, and presence of cough are all non-missing and are indicated as 'No' at OAV#1 or OAV#2, then the subject has resolution of symptoms at the respective Outcome Assessment Visit. Otherwise, resolution of symptoms is missing at the Outcome Assessment Visit.

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

The maximum severity at OAV #1 will be calculated based on the following rules:

- If a subject has missing data for the severity grade of any solicited event for two consecutive days or has missing data for more than two days from Day 1 to Day 5 then the most severe solicited event at OAV#1 will be missing.
- Otherwise if a subject has missing data for one or two non-consecutive days from Day 1 to Day 5 then the missing severity will be imputed as the maximum severity grade taken across the previous day and the day after the day with a missing severity. As a special case, for subjects missing severity for Day 1, the missing severity will be imputed as the Severity from Day 2. For subjects missing severity at Day 5 but not missing severity at Day 6, the missing severity will be imputed as the maximum of severity gradings from Day 4 and Day 6. For these subjects with severity grades (0 to 3) recorded or imputed for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 5, inclusive, the most severe solicited event at OAV#1

will be the maximum severity grade taken across all solicited events from Day 1 to Day 5.

- If a subject had any solicited event of severity grade 3 from Day 1 to Day 5, then the most severe solicited event at OAV#1 will be grade 3, regardless of the presence of missing data during that period.

In a similar manner, the maximum severity at OAV #2 will be calculated based on the following rules:

- If a subject has missing data for the severity grade of any solicited event for more than three consecutive days or has missing data for more than five days from Day 1 to Day 18 then the most severe solicited event at OAV#2 will be missing.
- Otherwise if a subject has missing data for five days or less and no more than three of them are consecutive Day 1 to Day 18 then the missing severity will be imputed as the maximum severity grade taken across the previous day and the day after the day with a missing severity. As a special case, for subjects missing severity for Day 1, the missing severity will be imputed as the Severity from Day 2. For subjects missing severity at Day 18, the missing severity will be imputed as the severity from Day 17. For these subjects with severity grades (0 to 3) recorded or imputed for every solicited event (irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis) from Day 1 to Day 18, inclusive, the most severe solicited event at OAV#2 will be the maximum severity grade taken across all solicited events from Day 1 to Day 18.
- If a subject had any solicited event of severity grade 3 from Day 1 to Day 18, then the most severe solicited event at OAV#2 will be grade 3, regardless of the presence of missing data during that period.

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

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

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

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

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

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

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

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

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

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

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

Else OCR at OAV#1 will be 1.

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

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

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

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

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

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

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

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

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

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

Else OCR at OAV#2 will be 1.

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

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

It will be assumed that all subjects have precisely five days of antibiotic use with the initial antibiotic prior to Day 1 (the day of the first dose of study product). Analysis involving comparisons of the number of days of antibiotic use will consider antibiotic use from Day 1 onwards. The number of days of antibiotic use is defined as the actual number of days of antibiotic use (any amount of study product that is not placebo, or any amount of other systemic antibiotic) from Day 1 to Day 5, inclusive, for OAV#1 and from Day 1 to Day 18 for OAV#2. For subjects that received placebo as study product, it is counted as the number of days of systemic antibiotic as determined solely from the concomitant medication form. For subjects that receive actual antibiotic as study product, it is counted as the number of days that the subject received any amount of either study product or a non-study systemic antibiotic, as determined

from the concomitant medication form. Note that missed doses of study product do not necessarily lower the number of days of antibiotic use as long as a separate dose of antibiotic (study product antibiotic or concomitant medication antibiotic) was received on that day. Extra doses of study product beyond the protocol specification of 10 doses count as normal toward the number of days of antibiotic use. The number of days of antibiotic use is missing (at both OAV#1 and OAV#2) if the product administration record was not completed / on record for the subject and the subject did not have antibiotic use during the study period recorded as a concomitant medication. If a subject does not have an OAV#1 or OAV#2, then number of days of antibiotic use at OAV#1 is missing. If a subject does not have an OAV#2, then number of days of antibiotic use at OAV#2 is missing. As exceptions, subjects that were hospitalized due to pneumonia or a complication of pneumonia or the died during the study period will have number of days of antibiotic use at OAV#1 or OAV#2 as 5 if randomized to the standard course or as 0 if randomized to short course if the number of days of antibiotic use at OAV#1 or OAV#2 is missing as defined above.

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

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

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

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

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

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

6.6. Interim Analyses and Data Monitoring

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

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

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

The DSMB will also be provided with the following:

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

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

6.6.1. Predicted Interval Plots (PIPs)

PIPs provide insight into the range of possible outcomes that can be expected for the final primary analysis under various assumptions (such as that the current observed treatment effect represents the true effect or that the null hypothesis represents the true effect). Using various assumptions, data is simulated from theoretical distributions to create multiple complete datasets representing complete datasets for the final analysis under the assumed reality. Details of PIPs and their interpretations can be found in the literature (Evans 2007, Li 2009).

For each assumption, one-hundred (100) 95% predicted intervals of the probability of higher DOOR in the 5-day treatment course at Outcome Assessment Visit #1 will be generated from 100 complete datasets. Each dataset will include the ITT analysis population for the interim analysis, plus additional simulated subjects to a total of 400 subjects in the dataset. Predicted intervals will be computed by inverting the Mann-Whitney U test (Section 8.2.2). The predicted intervals will be ordered by their corresponding point estimate of the probability of higher DOOR in the 5-day treatment course and shown graphically as forest plots. The 95% confidence interval generated in the ITT interim analysis of the probability of higher DOOR at Outcome Assessment Visit #1 will be overlaid on the forest plot. Comparisons of the predicted intervals to

the confidence interval show changes in precision of estimated probability (tightness of predicted intervals versus the confidence interval) as well as the expected distribution of location shifts of the estimated probability in the final analysis relative to the interim analysis, dependent on the assumptions used. Conditional power will be estimated as the percentage of predicted intervals with a lower bound that is greater than 0.5.

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

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

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

Under the alternative hypothesis assumption, each complete dataset is simulated in the following way. Multiple imputation will be used (Section 8.4.1) to create 100 datasets with complete data for DOOR at Outcome Assessment Visit #1 for enrolled subjects. For each of these 100 datasets, future subjects will be added to the analysis dataset. The number of future subjects added will be chosen to bring the total number of subjects (real and simulated combined) to 400 in the analysis dataset. The treatment ratio in the simulated subjects will be 1:1. The DOOR values for the future subjects in each dataset will be simulated by sampling with replacement from the overall (not by treatment) empirical distribution of DOOR values from the same dataset. All simulated subjects with a treatment assignment randomly chosen as the 5-day course will have the DOOR (rank) shifted by a value beta. The value beta will be chosen through a manual trial-and-error process such that the probability of higher DOOR in the 5-day subjects, comparing simulated subjects only, has a mean value of approximately 0.6 across all 100 datasets.

6.7. Multicenter Studies

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

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

6.8. Multiple Comparisons/Multiplicity

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

7. STUDY SUBJECTS

7.1. Disposition of Subjects

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

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

7.2. Protocol Deviations

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

8. EFFICACY EVALUATION

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

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

8.1. Primary Efficacy Analysis

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

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

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

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

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

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

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

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

Defining the following:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.2. Secondary Efficacy Analyses

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

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

The null hypothesis corresponding to this analysis is:

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

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

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

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

Defining the following:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Confidence intervals from inverting the Mann-Whitney U Test:

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

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

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

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

Confidence intervals using a non-parametric bootstrap:

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

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

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

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

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

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

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

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

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

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

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

Analysis will be performed as described in Section 8.2.2 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8 and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 0. As an exception, subjects in the short course arm with OCR missing for Outcome Assessment Visit #1 but not for Outcome Assessment Visit #2 will have the OCR for Outcome Assessment Visit #1 imputed as the Outcome Assessment Visit #2 value or as 5, whichever value is larger. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.) and their number of days of antibiotic use imputed if missing (see Section 6.5.6) as 5.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

difference in proportion on y-axis), together with 95% confidence intervals computed using the Newcombe method with continuity correction.

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

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

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

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

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

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

Results will be reported in Table 30.

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

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

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

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

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

Results will be reported in Table 31.

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

Analysis will be performed as described in Section 8.2.6 using the CC-V1 population. Results will be reported in Table 32 and Table 33.

8.2.6.4. Complete Case Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the CC-V2 population. Results will be reported in Table 34 and Table 35.

8.2.6.5. According-to-Protocol Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the ATP-V1 population. Results will be reported in Table 36 and Table 37.

8.2.6.6. According-to-Protocol Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the ATP-V2 population. Results will be reported in Table 38 and Table 39.

8.2.6.7. Worst Case Analysis of the OCR at Outcome Assessment Visit #1

Analysis will be performed as described in Section 8.2.6 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8. As an exception, subjects in the shorts course arm with OCR missing for Outcome Assessment Visit #1 but not for Outcome Assessment Visit #2 will have the OCR for Outcome Assessment Visit #1 imputed as the Outcome Assessment Visit #2 value or as 5, whichever value is larger. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.). Results will be reported in Table 40.

8.2.6.8. Worst Case Analysis of the OCR at Outcome Assessment Visit #2

Analysis will be performed as described in Section 8.2.6 using the ITT population with missing values imputed as follows. Subjects in the short course arm will have their ordinal clinical response imputed as 8. Subjects in the standard course arm will have their ordinal clinical response imputed as the value that would occur if all missing data was benign (no additional solicited events / cough / fever, etc.). Results will be reported in Table 41.

8.2.7. Additional Analysis of Cough

The proportion of subjects in each treatment group experiencing moderate or severe cough will be tabulated by day from Day 1 to Day 25 (as recorded from the memory aid), by visit, and overall, with 95% exact confidence intervals (Table 42). The proportion of subjects in each treatment group experiencing cough will also be tabulated by day from Day 1 to Day 25 (as recorded from the memory aid), by visit, and by severity level (Table 43 and Table 44). Finally, cough will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) (Table 45). Proportions for these derived binary variables will be reported along with 95% exact confidence intervals. Comparisons of proportions by treatment groups will be given as odds ratios (with

95% exact confidence intervals) and p-values from Fisher's Exact Tests. Cough severity will be listed by study day and study visit (Listing 15 and Listing 16).

8.3. Exploratory Efficacy Analyses

8.3.1. Complete Case Evaluation of DOOR at Outcome Assessment Visit #1, Minimum Required Difference in Days for Antibiotic Use "Tie-breaking" Varies k=1,2,3,4,5, or infinity

In the primary RADAR/DOOR analysis, if two subjects from separate treatment arms have an equal ordinal clinical response but a difference in the duration of antibiotic use of at least k=1 day, RADAR assigns a more favorable response to the subject with fewer days of antibiotic use. For a sensitivity analysis, the effect of increasing the minimum difference in the duration of antibiotic use (k=2,3,4, or 5, or infinity) before a favorable response is given to the subject with shorter duration of antibiotic use will be explored. The analysis of RADAR/DOOR with k=infinity is equivalent to comparison of OCR without regard for number of days of antibiotic use, and is included here for comparative purposes. For each value of k, bootstrapped confidence intervals of the probability of more favorable DOOR due to assignment to the 5-day antibiotic course will be computed and plotted versus k. Analysis will be performed separately for DOOR at Outcome Assessment Visit #1 and DOOR at Outcome Assessment Visit #2. Analyses will be performed using CC-V1/CC-V2 cohorts. Results will be reported in Table 46 and Figure 23.

8.3.2. Stratified (ITT) Analyses of DOOR at Outcome Assessment Visit #1

Analysis of DOOR at Outcome Assessment Visit #1 as described in Section 8.1.1 will be performed separately for each level of each stratification variable (e.g. an analysis of all subjects of age <24 months at enrollment, and a separate analysis of all subjects of age 24-71 months at enrollment) and by clinical site. Results will be reported Table 47.

8.3.3. As Treated Analysis of Effect of Number of Days of Antibiotic Use on OCR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

The analysis will be performed using the subset of the CC-V1 analysis population that did not receive off-study systemic antibiotic unrelated to pneumonia prior to Outcome Assessment Visit #1. The justification for excluding subjects with unrelated antibiotic use is that subjects receiving unrelated antibiotics are at risk for both improved outcomes due to ongoing antibiotic use as well as increased side effects related to antibiotics administration. The effect of the number of days of antibiotic use at Outcome Assessment Visit #1 on OCR at Outcome Assessment Visit #1 will be analyzed using a proportional odds model that simultaneously uses all cumulative logits (Agresti 2003).

Let **K** be the set of distinct OCR values observed at Outcome Assessment Visit #1, with the exception that the highest (worst) distinct value observed is not included in the set.

Let Y_i = the OCR of subject i at Outcome Assessment Visit #1.

Let X_i = the number of days of antibiotic use at Outcome Assessment Visit #1 for subject *i*.

α_k, where k ϵ K, and β are parameters to be simultaneously estimated through maximum likelihood methods.

Then, proportional odds model with cumulative logits is defined as

$\text{Logit}\,[P(Y_i > k)] = \alpha_k + \beta X_i\,, \qquad k \in \mathbf{K}$

The following gives the interpretation of the model. Suppose D is any non-negative integer.

Then, $\log[\text{odds}(OCR>k \mid X_i = D+1) / \text{odds}(OCR>k \mid X_i = D)] = \beta$.

That is, for any *k*, where *k* is from the set of observed OCR values at Outcome Assessment Visit #1 besides the highest observed value, e^{β} gives the odds ratio of an OCR at Outcome Assessment Visit #1 greater than *k* for the effect of one additional day of use of antibiotic.

It should be stated clearly that this analysis is "as treated" rather than "as randomized." As such, causality cannot be inferred from a statistically significant association. This is especially true if subjects receiving off-study antibiotic not unrelated to the prior diagnosis of pneumonia are observed during the study. Such subjects will have a higher OCR and will also likely have more days of antibiotic use.

This analysis will be repeated using the subset of the CC-V2 analysis population that did not receive off-study systemic antibiotic unrelated to pneumonia prior to Outcome Assessment Visit #2. The effect of the number of days of antibiotic use at Outcome Assessment Visit #2 on OCR at Outcome Assessment Visit #2 will be analyzed using logistic regression with a proportional odds assumption. Results from both analyses will be summarized in Table 48. The odds ratio for the proportional odds of an OCR at Outcome Assessment Visit #1 greater than k for the effect of one additional day of use of antibiotic will be reported with a 95% Wald confidence interval and p-value from a Wald test. For $p<0.05$, an association between OCR and the number of days of antibiotic use, as treated, will be concluded.

8.4. Imputation of Missing Data

8.4.1. Multiple Imputation of Missing Ordinal Clinical Response and DOOR at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

Several analyses, including the primary analysis, depend on multiple imputation of DOOR or OCR at Outcome Assessment Visit #1 or Outcome Assessment Visit #2. Multiple imputations of each of these missing endpoints will be performed independently, and each subject will have their missing endpoints imputed independently of other subject's imputations using a subject-specific imputation model.

As a first step to multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for DOOR at Outcome Assessment Visit #1 and OCR at Outcome Assessment Visit #1 is below.

- Indicator of subject enrolled at the site with the second most number of subjects enrolled (binary indicator)
- Indicator of subject enrolled at the site with the third most number of subjects enrolled (binary indicator)

- Indicator of subject enrolled at the site with the least number of subjects enrolled (binary indicator)
  - Note: the site with the most number of subjects enrolled is reference for site. Language is written to allow for an arbitrary number of sites. In the event of a number of ties for the number of subjects enrolled, tied sites will be ordered in ascending alphanumeric order in the list of model variables.
- Indicator of amoxicillin (not amoxicillin placebo) as study treatment (binary indicator)
- Indicator of amoxicillin-clavulanate (not amoxicillin-clavulanate placebo) as study treatment (binary indicator)
- Indicator of cefdinir (not cefdinir placebo) as study treatment (binary indicator)
  - Note: placebo is the reference group for study treatment
- Indicator for amoxicillin-clavulanate as initial antibiotic (binary indicator)
- Indicator for cefdinir as initial antibiotic (binary indicator)
  - Note: amoxicillin is the reference group for initial antibiotic
- Indicator for age $\geq$ 2 years at enrollment (binary indicator)
- Indicator for initial treatment site for pneumonia at an emergency department (binary indicator)
- OCR at Outcome Assessment Visit #2 (imputed OCRs will not be used)
- Severity of cough on Day 1 as recorded on Solicited Events form (0, 1, 2, or 3)
  - Note: amoxicillin is the reference group for initial antibiotic
- Severity of most severe solicited event (besides cough) on Day 1(0, 1, 2, or 3)
  - Note: Some missing values for Day 1 will first be imputed as described in Section 6.5.4
- Severity of cough on Day 2 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 2 (0, 1, 2, or 3)
  - Note: Some missing values for Day 2 will first be imputed as described in Section 6.5.4
- Severity of cough on Day 3 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 3 (0, 1, 2, or 3)
  - Note: Some missing values for Day 3 will be first imputed as described in Section 6.5.4
- Severity of cough on Day 4 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 4 (0, 1, 2, or 3)
  - Note: Some missing values for Day 4 will first be imputed as described in Section 6.5.4

- Severity of cough on Day 5 as recorded on Solicited Events form (0, 1, 2, or 3)
- Severity of most severe solicited event (besides cough) on Day 5 (0, 1, 2, or 3)
  - Note: Some missing values for Day 5 will first be imputed as described in Section 6.5.4

For DOOR and OCR at Outcome Assessment Visit #2, the complete list of model variables is identical to the above, but with OCR at Outcome Assessment Visit #2 replaced with OCR at Outcome Assessment Visit #1. Additionally, cough severity and most severe solicited event are listed up to Day 18 rather than Day 5.

The actual list of model variables for each subject-specific imputation model will follow the ordering above but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification given in the pseudo-code and subjects must be processed in the order described in the pseudo-code. OCR will simultaneously be imputed with DOOR at each respective Outcome Assessment Visit. The pseudo-code is in terms of the Outcome Assessment Visit #1 endpoints, but the general logic is also applicable to the Outcome Assessment Visit #2 endpoints (with references to "V1" replaces with references to "V2").

```
DEFINE i=index variable for subjects having DOOR imputed.
      Subjects requiring imputation are sorted in ascending order
      by PATID.
DEFINE N=number of subjects requiring imputation
DEFINE g&i=analysis dataset containing predictors and DOOR for
       CC-V1 subjects as well as subject i (only one subject not in
       CC-V1 included).  Note that CC-V1 subjects that are missing a
       value
       for one or more variables in the subject-specific imputation
       model are excluded.
DEFINE imp_g&i = g&i, with 20 imputed values for the missing DOOR
      added by PROC MI
DEFINE &&modelVars_&i = list of observed variables in subject i, to
      be used for imputation of DOOR and OCR.


%do i=1 %to &N;
PROC MI data=g&i out=imp_g&i seed=1200&i NIMPUTE=20 noprint;
      var &&modelVars_&i DOOR OCR;
      monotone reg(DOOR_V1 = &&modelVars_&i);
      monotone reg(OCR_V1 = &&modelVars_&i);
```

```
run;

%end;


imp_g&i will be subset to contain only rows for the subjects with
imputed DOOR and merged together and with CC-V1 data to create the
twenty complete multiply imputed datasets
**********************************************************************
```

9. SAFETY EVALUATION

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

9.1. Demographic and Other Baseline Characteristics

Summaries of age, gender, enrollment site, ethnicity, race, initial antibiotic therapy, initial treatment locations, and age group (<24 months vs. 24-71 months) will be presented by site (Table 9 and Table 10) or by treatment group and overall (Table 11 and Table 12). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, a subject's guardians may designate the subject as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Summaries of subject's medical history will be presented by MedDRA® system organ class (SOC) and treatment group (Table 13).

Individual subject listings for all demographics (Listing 5) and pre-existing medical conditions (Listing 6) will be presented.

9.1.1. Concurrent Illnesses and Medical Conditions

Physical assessment findings from the enrollment visit, and any follow up visits, will be included in Listing 11.

9.1.2. Prior and Concurrent Medications

All concomitant medications taken within 30 days of signing the informed consent or during the study period will be recorded. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. A by-subject listing of concomitant medication use will be presented (Listing 12). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group (Table 56).

9.2. Measurements of Treatment Compliance

Treatment was administered to subjects at their homes by a parent or caregiver. The number of subjects receiving the first dose of study product will be tabulated by site, treatment group, and time period (Table 6). The number of doses of study product administered will be presented by treatment group (Table 7, Listing 7).

9.3. Adverse Events

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

9.3.1. Solicited Events

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

Solicited events were recorded for trial Days 1-25, or until study completion or termination, as the maximum severity for each day. Target solicited events include irritability, vomiting, diarrhea, allergic reaction, stomatitis, and candidiasis.

The proportion of subjects in each treatment group experiencing each solicited event with mild or greater severity will be tabulated by day and overall (Table 49 and Table 50). The proportion of subjects in each treatment group experiencing each solicited event will also be tabulated by day and severity level (Table 51 and Table 52). Finally, solicited events will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none or mild versus moderate or severe) (Table 53). Proportions for these derived binary variables will be reported along with 95% exact confidence intervals. Comparisons of proportions by treatment groups will be given as odds ratios (with 95% exact confidence intervals) and p-values from Fisher's Exact Tests.

The maximum severity occurrence of each solicited event and cough (proportion of subjects for each severity level) will be plotted for each solicited adverse event (Figure 24). Solicited events by subject will also be presented (Listing 8).

9.3.2. Unsolicited Adverse Events

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

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

Detailed narratives will be given for any deaths or other protocol-defined SAEs that occurred during the study. Listings of SAEs will be presented including subject ID, AE description, AE onset date/end date, reason reported as an SAE, relationship to treatment, alternate etiology if not related, outcome, and duration of event (days) (Listing 9). SAEs will also be listed in Table 54.

9.5. Vital Signs and Physical Evaluations

Vital signs will be taken at the enrollment visit, Outcome Assessment Visit #1, and Outcome Assessment Visit #2. For each visit, by treatment group, the mean, median, standard deviation, min, and max of vital sign will be calculated for temperature, respiration rate, and pulse (Table 55). Individual vital signs measurements will be listed (Listing 10).

9.6. Concomitant Medications

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

will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented. The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and treatment group for the Safety population (Table 56).

9.7. Other Safety Measures

The number and percent of subjects visiting an emergency department, primary care provider, study physician, urgent care, or having some other type of medically attended visit due to worsening study pneumonia will be presented together with whether the subject received antibiotic, surgical treatment, or was hospitalized due to pneumonia or a complication of pneumonia (Table 57). Medically attended visits will also be listed (Listing 13 and Listing 14). Presence of fever will be listed by visit (Listing 17 and Listing 18).

10. OTHER ANALYSES

No other analyses are planned.

11. REPORTING CONVENTIONS

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

12. TECHNICAL DETAILS

SAS version 9.3 or above or R version 3.2 or above will be used to perform analyses and to generate all tables, figures and listings.

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

Changes in the Conduct of the Study

Enrollment into the study was initiated under protocol version 2.0. Substantive changes to the protocol after study initiation are provided below.

Substantive changes in protocol version 3.0

- Removed 200mg/5mL amoxicillin and 200mg/5mL amoxicillin-clavulanate as possible dose strengths under Protocol Section 6.1.2. No subjects were prescribed under this dose.
- Clarified timing of interim analysis to be after at least 30% of the targeted subjects have completed the study instead of approximately 30%.

Changes to the Planned Analyses

There are no changes to the planned analyses as described in the protocol.

14. REFERENCES

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15. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

10.2 Protocol Deviations

Table 2: Distribution of Protocol Deviations by Category, Type and Treatment Group

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

12.2.2 Displays of Adverse Events

Table 3: Solicited Adverse Event Grading Scale

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

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 4: Subject Disposition by Treatment Group

Subject Disposition	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received First Dose of Treatment	x	xx	x	xx	x	xx
Received All Scheduled Treatment[a]	x	xx	x	xx	x	xx
Completed All Future Use Sample Collection						
Completed Outcome Assessment Visit #1 (Study Day 6-10)[a]						
Completed Outcome Assessment Visit #2 (Study Day 19-25) [a]						

[a] Refer to Listing 1 for reasons subjects discontinued or terminated early.
[b] Refer to Listing 4 for reasons subjects are excluded from the Analysis populations.

Table 5: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
ITT[1]	Any Reason	x	xx	x	xx	x	xx
	Became ineligible before taking study product						
CC-V1[2]	Any Reason						
	Subject not treated with study product						
	Early termination before Outcome Assessment Visit #1						
	-Reason 1 for termination						
	-Reason 2 for termination						
	Completed Outcome Assessment Visit #1, but Missing DOOR Component						
	-Adequate Clinical Response						
	-Resolution of Symptoms						
	-Solicited Event Severity Days 1-5						
	-Number of Days of Antibiotic Use						
CC-V2	Any Reason						
	Subject not treated with study product						
	Early termination before Outcome Assessment Visit #2						
	-Reason 1 for termination						
	-Reason 2 for termination						
	Completed Outcome Assessment Visit #2, but Missing DOOR Component						
	-Adequate Clinical Response						
	-Resolution of Symptoms						
	-Solicited Event Severity Days 1-8						
	-Number of Days of Antibiotic Use						
ATP-V1[3]	Any Reason						
	The subject was excluded from CC-V1 cohort.						

Table 5: Analysis Populations by Treatment Group *(continued)*

Analysis Populations	Reason Subjects Excluded	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
	Subject did not receive at least one dose of study product each day from Day 1 to Day 5						
	Major protocol deviation						
	-Outcome Assessment Visit #1 occurred out of the protocol defined window of Day 6-10						
	-Outcome Assessment Visit #1 did not occur as an in-person visit						
ATP-V2	Any Reason						
	The subject was excluded from CC-V2 cohort.						
	Subject did not receive at least one dose of study product each day from Day 1 to Day 5						
	Major protocol deviation						
	-Outcome Assessment Visit #2 occurred out of the protocol defined window of Day 19-25						
	-Outcome Assessment Visit #2 did not occur as an in-person visit						

[1] ITT = Intent-to-Treat
[2] CC = Complete Case
[3] ATP = According-to-Protocol

Table 6: Dates of First Treatment by Site and Treatment Group

Site	Treatment Group	July 2016 - June 2017	July 2017 - June 2018	July 2018 - June 2019	July 2019 - November 2019
Children's Hospital of Philadelphia	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Children's Hospital of Pittsburgh	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Cincinnati Children's Hospital	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Duke University	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Vanderbilt University	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Any Site	Standard Course	x	x	x	x
	Short Course	x	x	x	x
Any	Any	x	x	x	x

[Programming Note: Rows will be added for additional sites that enroll at least one subject, as needed.]

Table 7: Treatment Compliance by Treatment Group

	Number of Doses Administered n (%)												
Treatment Group	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Standard Course (N=X)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Short Course (N=X)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 8: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible[1]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x
Inclusion	Any inclusion criterion	x
	[inclusion criterion 1]	x
	[inclusion criterion 2]	x
	[inclusion criterion 3]	x
Exclusion	Any exclusion criterion	x
	[exclusion criterion 1]	x
	[exclusion criterion 2]	x
	[exclusion criterion 3]	x

[1] More than one criterion may be marked per subject.

14.1.2 Demographic Data by Study Group

Table 9: Summary of Categorical Demographic and Baseline Characteristics by Site

Demographic Category	Characteristic	Children's Hospital of Philadelphia (N=X)		Children's Hospital of Pittsburgh (N=X)		Cincinnati Children's Hospital (N=X)		Duke University (N=X)		Vanderbilt University (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x
Initial Antibiotic	Amoxicillin	x	x	x	x	x	x	x	x	x	x	x	x
	Amoxicillin-Clavulanate	x	x	x	x	x	x	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x	x	x	x	x	x	x

[Programming Note: Columns will be added for additional sites that enroll at least one subject, as needed.]

Table 10: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	Children's Hospital of Philadelphia (N=X)	Children's Hospital of Pittsburgh (N=X)	Cincinnati Children's Hospital (N=X)	Duke University (N=X)	Vanderbilt University (N=X)	All Subjects (N=X)
Age (Months)	Mean	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x

[Programming Note: Columns will be added for additional sites that enroll at least one subject, as needed.]

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Demographic Category	Characteristic	Standard Course (N=X)		Short Course (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	x	x	x	x	x
	Female	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Initial Antibiotic	Amoxicillin	x	x	x	x	x	x
	Amoxicillin-Clavulanate	x	x	x	x	x	x
	Cefdinir	x	x	x	x	x	x
Initial Site of Treatment	ED	x	x	x	x	x	x
	Out-Patient/Urgent Care	x	x	x	x	x	x
Age Group	<24 Months	x	x	x	x	x	x
	24-71 Months	x	x	x	x	x	x
Clinical Trial Site	Children's Hospital of Philadelphia	x	x	x	x	x	x
	Children's Hospital of Pittsburgh	x	x	x	x	x	x
	Cincinnati Children's Hospital	x	x	x	x	x	x
	Duke University	x	x	x	x	x	x
	Vanderbilt University	x	x	x	x	x	x

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Statistic	Standard Course (N=X)	Short Course (N=X)	All Subjects (N=X)
Age (Months)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

14.1.3 Prior and Concurrent Medical Conditions

Table 13: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

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

Note: N=Number of subjects enrolled; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy/Immunogenicity Data

Table 14: Primary ITT Analysis of DOOR at Outcome Assessment Visit #1

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx

1 Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR. Confidence interval obtained through inversion of the F-test used to compute the p-value.
2 P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 15: Primary ITT Analysis of DOOR at Outcome Assessment Visit #2

Statistic	Value
Subjects with all DOOR components measured – n (%)	x (x)
Subjects with one or more DOOR components imputed – n (%)	x (x)
Pr(Higher DOOR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx

1 Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal DOOR. Confidence interval obtained through inversion of the F-test used to compute the p-value.
2 P-value boundary of 0.05 is used to conclude statistical significance. It is important to note that conclusions from DOOR analyses must rely on a detailed assessment of the DOOR components as well as consideration of sensitivity analyses, in addition to the statistical test described in this table.

Table 16: Sensitivity Analyses of DOOR at Outcome Assessment Visit #1

Analysis	Pr (Higher DOOR)[1]	Normal Approx. 95% CI[2]	Bootstrapped 95% CI[3]	P-value[4]
Complete Case (CC-V1)				
According-to-Protocol (ATP-V1)				
Worst Case (ITT)				

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR.
[2] Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance Var(U)=n1n2(n1+n2+1)/12.
[3] 2.5th and 97.5th percentiles of Pr (Higher DOOR) obtained by repeatedly re-sampling of the empirical distributions of DOOR scores by treatment arm.
[4] P-value obtained by Mann-Whitney U Test.

Table 17: Sensitivity Analyses of DOOR at Outcome Assessment Visit #2

Analysis	Pr (Higher DOOR)[1]	Normal Approx. 95% CI[2]	Bootstrapped 95% CI[3]	P-value[4]
Complete Case (CC-V2)				
According-to-Protocol (ATP-V2)				
Worst Case (ITT)				

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal DOOR.
[2] Obtained through using inversion of the Mann-Whitney U test with a normal approximation and assuming the null hypothesis distribution variance Var(U)=n1n2(n1+n2+1)/12.
[3] 2.5th and 97.5th percentiles of Pr(Higher DOOR) obtained by repeatedly re-sampling of the empirical distributions of DOOR scores by treatment arm.
[4] P-value obtained by Mann-Whitney U Test.

Table 18: Risk of Mild, Moderate, or Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 19: Risk of Moderate or Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 20: Risk of Severe Solicited Event from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 5.
[1] P-value obtained by Fisher Exact Test.

Table 21: Risk of Mild, Moderate, or Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 22: Risk of Moderate or Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 23: Risk of Severe Solicited Event from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Risk Difference		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Any Event									
Irritability									
Vomiting									
Diarrhea									
Allergic Reaction									
Stomatitis									
Candidiasis									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of solicited events recorded from Day 1 to Day 18.
[1] P-value obtained by Fisher Exact Test.

Table 24: Lack of Resolution of Symptoms and Its Components at Outcome Assessment Visit #1 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Resolution of Symptoms									
Fever[2]									
Elevated respiratory rate[3]									
Cough[4]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population and the respective treatment group with complete records of fever, elevated respiratory rate, and cough at Outcome Assessment Visit #1.
[1] P-value obtained by Fisher Exact Test.
[2] As defined in Section 6.5.2 of the SAP.
[3] Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit.
[4] Presence of cough Grade 2 or 3 at the Outcome Assessment Visit.

Table 25: Lack of Resolution of Symptoms and Its Components at Outcome Assessment Visit #2 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Resolution of Symptoms									
Fever[2]									
Elevated respiratory rate[3]									
Cough[4]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population and the respective treatment group with complete records of fever, elevated respiratory rate, and cough at Outcome Assessment Visit #2.
[1] P-value obtained by Fisher Exact Test.
[2] As defined in Section 6.5.2 of the SAP.
[3] Elevated respiratory rate (RR >50 breaths/minute for children <24 months of age and >40 breaths/minute for children 24-71 months of age) at the time of the Outcome Assessment Visit.
[4] Presence of cough Grade 2 or 3 at the Outcome Assessment Visit.

Table 26: Risk of Lack of Adequate Clinical Response and Its Components from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Adequate Clinical Response									
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[3]									
Receipt of Non-Study Antibiotic[4]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
[3] For pneumonia or treatment for a complication of pneumonia, including but not limited to drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
[4] For pneumonia or treatment for a complication of pneumonia. Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

Table 27: Any Receipt of Non-Study Antibiotics and Medically Attended Visits from Day 1 to Day 5 (CC-V1 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[2]									
Receipt of Non-Study Antibiotic[2]									

Note: N=X indicates the number of subjects in the CC-V1 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For any reason.

Table 28: Risk of Lack of Adequate Clinical Response and Its Components from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
Lack of Adequate Clinical Response									
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[3]									
Receipt of Non-Study Antibiotic[4]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For persistent or worsening pneumonia that occurs after randomization and receipt of at least one dose of study drug.
[3] For pneumonia or treatment for a complication of pneumonia, including but not limited to drainage of pleural fluid, placement of a chest tube, video assisted thoracoscopic surgery, or thoracotomy procedures.
[4] For pneumonia or treatment for a complication of pneumonia. Receipt of a non-study antibiotic will not be regarded as satisfying this definition if it is related to a new diagnosis that is unrelated to the prior diagnosis of pneumonia.

Table 29: Any Receipt of Non-Study Antibiotics or Medically Attended Visit from Day 1 to Day 18 (CC-V2 Cohort) by Treatment Group

Event	Standard Course (N=X)			Short Course (N=X)			Difference in Proportion		P-value[1]
	n	%	95% CI	n	%	95% CI	%	95% CI	
ED or Clinic Visit[2]									
Hospitalization[2]									
Surgical Procedure[2]									
Receipt of Non-Study Antibiotic[2]									

Note: N=X indicates the number of subjects in the CC-V2 analysis population.
[1] P-value obtained by Fisher Exact Test.
[2] For any reason.

Table 30: ITT Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 31: ITT Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 32: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (CC-V1)

Statistic	Value
CC-V1 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 33: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (CC-V1) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 34: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (CC-V2)

Statistic	Value
CC-V2 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.

[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.

[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 35: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (CC-V2) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 36: According-to-Protocol Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ATP-V1)

Statistic	Value
ATP-V1 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
Test No Difference in OCR, P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 37: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ATP-V1) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 38: According-to-Protocol Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ATP-V2)

Statistic	Value
ATP-V2 Subjects (N=X)	
Standard Course – n (%)	x (x)
Short Course – n (%)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 39: Complete Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ATP-V2) - Comparison of Distributions

	Ordinal Clinical Response							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Standard Course (N=X) – n (%)								
Short Course (N=X) – n (%)								
Mean Score Statistic (Q_S) P-Value: x.xxx								

Table 40: Worst Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #1 (ITT Cohort)

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
Test No Difference in OCR, P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #1 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #1 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 41: Worst Case Analysis of Ordinal Clinical Response at Outcome Assessment Visit #2 (ITT Cohort)

Statistic	Value
Subjects with non-missing OCR– n (%)	
Standard Course (N=X)	x (x)
Short Course (N=X)	x (x)
Pr(Lower OCR in Short-Course)[1] (95% CI)	x.x (x.x – x.x)
P-value[2]	x.xxx
Non-inferiority[3]	Yes/No

[1] Probability of Lower OCR in Short-Course Arm at Outcome Assessment Visit #2 + 0.5 Probability of Equal OCR. Confidence interval obtained through inversion of the F-test used to compute the p-value. In contrast to DOOR, lower OCRs are more favorable.
[2] Test of null hypothesis "Pr(OCR at Outcome Assessment Visit #2 is better in short-course) + 0.5 Pr(OCR at Outcome Assessment Visit #2 is equal) = 0.5". P-value boundary of 0.05 is used to conclude statistical significance.
[3] Non-inferiority is concluded if the lower bound of the confidence interval for Pr(Lower OCR) is greater than 0.40.

Table 42: Number and Percentage of Subjects Experiencing Moderate or Severe Cough by Day and Treatment Group

Study Day or Visit	Standard Course - Moderate or Severe Cough				Short Course - Moderate or Severe Cough			
	N	n	%	95% CI	N	n	%	95% CI
Overall	x	x	x	(x, x)	x	x	x	(x, x)
OAV #1	x	x	x	(x, x)	x	x	x	(x, x)
OAV #2	x	x	x	(x, x)	x	x	x	(x, x)
Day 1	x	x	x	(x, x)	x	x	x	(x, x)
Day 2	x	x	x	(x, x)	x	x	x	(x, x)
Day 3	x	x	x	(x, x)	x	x	x	(x, x)
Day 4	x	x	x	(x, x)	x	x	x	(x, x)
Day 5	x	x	x	(x, x)	x	x	x	(x, x)
Days 6-9	x	x	x	(x, x)	x	x	x	(x, x)
Day 10-13	x	x	x	(x, x)	x	x	x	(x, x)
Day 14-18	x	x	x	(x, x)	x	x	x	(x, x)
Day 19-25	x	x	x	(x, x)	x	x	x	(x, x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 43: Number and Percentage of Subjects Experiencing Coughing by Maximum Severity and Treatment Group – Standard Course

Severity	Standard Course								
	Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 44: Number and Percentage of Subjects Experiencing Coughing by Maximum Severity and Treatment Group – Short Course

Severity	Short Course								
	Day 1 (N=X) n (%)	**Day 2 (N=X) n (%)**	**Day 3 (N=X) n (%)**	**Day 4 (N=X) n (%)**	**Day 5 (N=X) n (%)**	**Days 6-9 (N=X) n (%)**	**Days 10-13 (N=X) n (%)**	**Days 14-18 (N=X) n (%)**	**Days 19-25 (N=X) n (%)**
None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with at least one severity grade collected for cough on the respective day or days.

Table 45: Number and Percentage of Subjects Experiencing Cough of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group

Severity	Standard Course (N=X)		Short Course (N=X)		Odds Ratio (95% CI)	P-Value
	n (%)	95% CI	n (%)	95% CI		
Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

Table 46: CC-V1 Evaluation of DOOR at Outcome Assessment Visit #1, Minimum Required Difference in Days for Antibiotic Use "Tie-Breaking" Varies k=1,2,3,4,5, or Infinity

k	Pr(Higher DOOR)[1]	95% CI	P-value
1	x.x	(x.x – x.x)	x.x
2			
3			
4			
5			
∞			

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR

Table 47: ITT Evaluation of DOOR at Outcome Assessment Visit #1, Analysis By Stratification Variable and Clinical Site

Variable	Level	Pr(Higher DOOR)[1]	95% CI	P-value
Age (Months)	<24	x.x	(x.x – x.x)	x.x
	24-71			
Initial Site of Treatment	ED			
	Out-Patient / Urgent Care			
Initial Antibiotic	Cefdinir			
	Amoxicillin			
	Amoxicillin Clavulanate			
Clinical Site	Children's Hospital of Philadelphia			
	Children's Hospital of Pittsburgh			
	Cincinnati Children's Hospital			
	Duke University			
	Vanderbilt University			

[1] Probability of Higher DOOR in Short-Course Arm at Outcome Assessment Visit #1 + 0.5 Probability of Equal DOOR

[Programming Note: Rows will be added for additional sites that enroll at least one subject, as needed.]

Table 48: As Treated Analysis of Association between Ordinal Clinical Response and the Number of Days of Antibiotic Use at Outcome Assessment Visit #1 and Outcome Assessment Visit #2

Outcome Assessment Visit[1]	Proportional Odds[2] Odds Ratio for 1 Additional Day of Antibiotic Use	95% CI	P-value
#1	x.xx	(x.xx, x.xx)	x.xxx
#2	x.xx	(x.xx, x.xx)	x.xxx

[1] Analysis at Outcome Assessment Visit #1 uses the subset of the CC-V1 analysis population that did not receive systemic antibiotic unrelated to pneumonia on or prior to Day 5. Analysis at Outcome Assessment Visit #2 uses the subset of the CC-V2 analysis population that did not receive systemic antibiotic unrelated to pneumonia on or prior to Day 18.

[2] Odds ratio of an OCR at Outcome Assessment Visit #1 greater than k for the effect of one additional day of use of antibiotic, where k is any observed OCR value (1, 2, 3, …) besides the highest observed value.

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.1.1 Solicited Adverse Events

Table 49: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Treatment Group - Standard Course

Standard Course																																
Symptom	**Day 1 (N=X)**			**Day 2 (N=X)**			**Day 3 (N=X)**			**Day 4 (N=X)**			**Day 5 (N=X)**			**Day 6-9 (N=X)**			**Day 10-13 (N=X)**			**Day 14-18** (N=X)			**Day 19-25 (N=X)**			**Day 1-25 (N=X)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Irritability																														
Vomiting																														
Diarrhea																														
Allergic Reaction																														
Stomatitis																														
Candidiasis																														

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table with similar format:

Table 50: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Treatment Group – Short Course

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Standard Course

Symptom	Severity	Standard Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Irritability	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Vomiting	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Diarrhea	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Allergic Reaction	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Stomatitis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Standard Course *(continued)*

Symptom	Severity	Standard Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Candidiasis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table 52: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Short Course

Symptom	Severity	Short Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Irritability	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Vomiting	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Diarrhea	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Allergic Reaction	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Stomatitis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

Table 52: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Treatment Group – Short Course *(continued)*

Symptom	Severity	Short Course								
		Day 1 (N=X) n (%)	Day 2 (N=X) n (%)	Day 3 (N=X) n (%)	Day 4 (N=X) n (%)	Day 5 (N=X) n (%)	Days 6-9 (N=X) n (%)	Days 10-13 (N=X) n (%)	Days 14-18 (N=X) n (%)	Days 19-25 (N=X) n (%)
Candidiasis	None	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mild	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Moderate	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Severe	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)

N = Number of subjects in the Safety Analysis Population in the respective treatment group and with severity grades collected for each solicited symptom on the respective day or days.

Table 53: Number and Percentage of Subjects Experiencing Solicited Adverse Events of Mild Severity or Greater, Moderate Severity or Greater, or Severe Severity Over the Follow-up Period by Treatment Group

Symptom	Severity	Standard Course (N=X)		Short Course (N=X)		Odds Ratio (95% CI)	P-Value
		n (%)	95% CI	n (%)	95% CI		
Any Symptom	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Irritability	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Vomiting	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Diarrhea	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Allergic Reaction	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Stomatitis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
Candidiasis	Mild or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Moderate or Greater	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx
	Severe	x (x)	(x, x)	x (x)	(x, x)	x.x (x.x, x.x)	x.xxx

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 54: Listing of Serious Adverse Events

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

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Laboratory Data Over Time

Not applicable

14.3.5 Displays of Laboratory Results

Not applicable

14.3.6 Displays of Vital Signs

Table 55: Summary of Vital Signs by Visit and Treatment Group

		Enrollment Visit		Outcome Assessment Visit #1		Outcome Assessment Visit #2	
		Standard Course	Control	Standard Course	Control	Standard Course	Control
Temperature (°F)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Respiratory Rate (breaths/min.)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx
Pulse (beats/min.)	N	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Std	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	x	x	x	x	x	x
	Min, Max	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx	xx,xx

14.4 Summary of Concomitant Medications

Table 56: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

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

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

Table 57: Medically Attended Visits

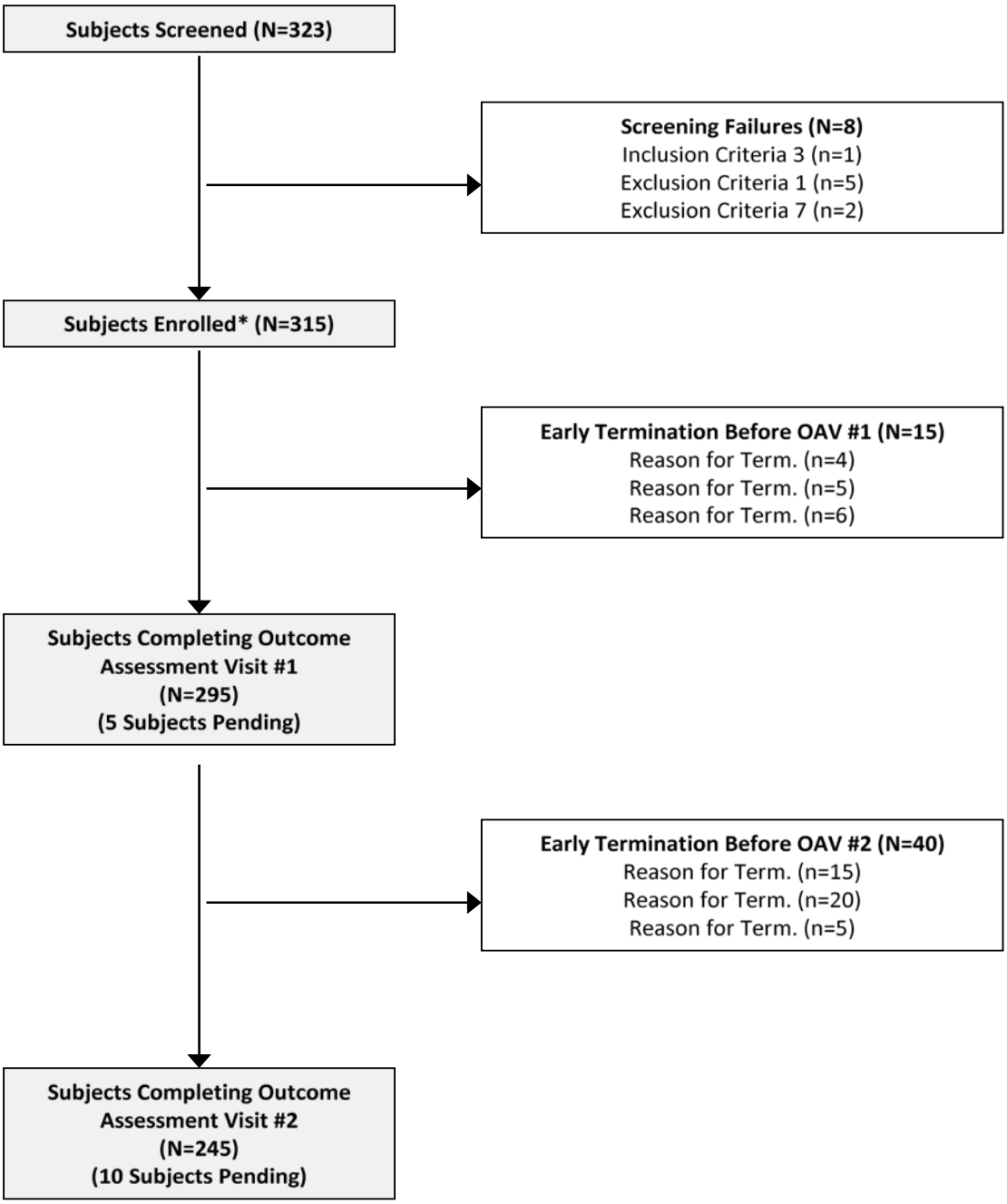
	Day 1-5		Day 6-18	
	Standard Course n (%) (N=X)	**Short Course n (%) (N=X)**	**Standard Course n (%) (N=X)**	**Short Course n (%) (N=X)**
Emergency Department Visit[1]				
Primary Care Provider Visit[1]				
Study Physician Visit[1]				
Urgent Care Visit[1]				
Other Medically Attended Visit[1]				
Additional Antibiotic Received[2]				
Drainage of pleural fluid[2]				
Placement of a chest tube[2]				
Video assisted thoracoscopic surgery[2]				
Thoracotomy procedure[2]				
Any other surgical procedure[2]				
Hospitalization[2]				

1 Visit associated with worsening study pneumonia.
2 For pneumonia or a complication of pneumonia.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

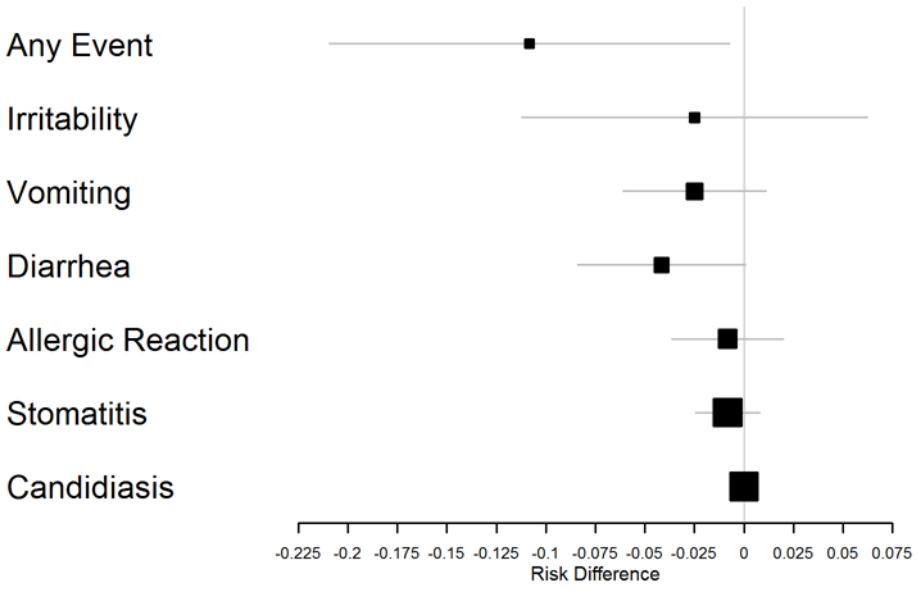
Figure 2: CONSORT Flow Diagram



*All enrolled subjects will be evaluable for the primary (ITT) analysis.

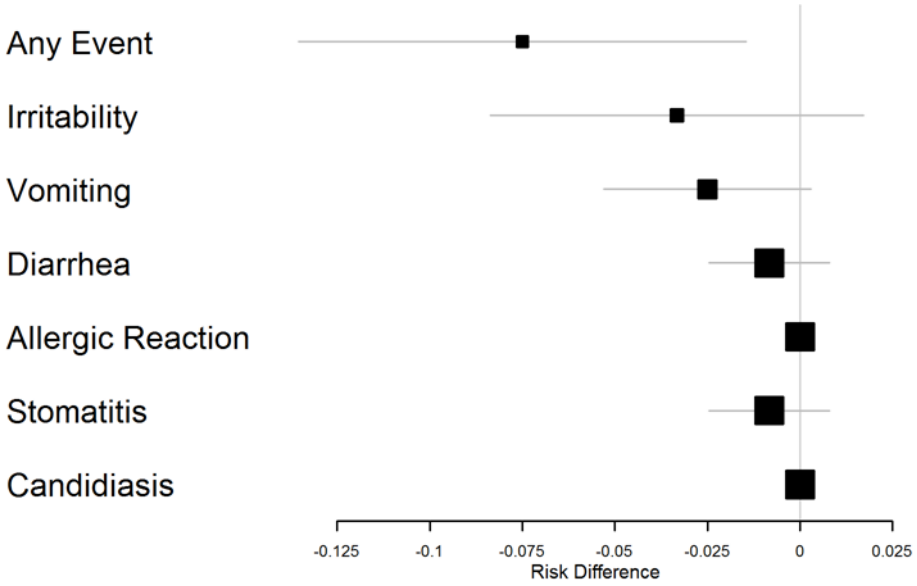
[Programming Note: Diagram will include breakdown by treatment arm and will add the 'Eligible but not Enrolled' category under subjects screened.]

Figure 3: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Mild, Moderate, or Severe - CC-V1 Population



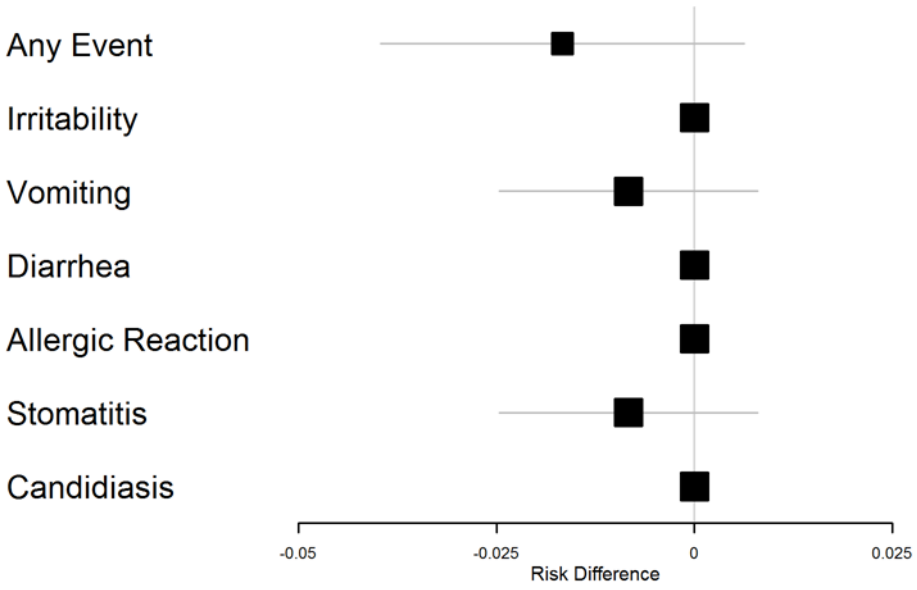
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 4: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Moderate or Severe - CC-V1 Population



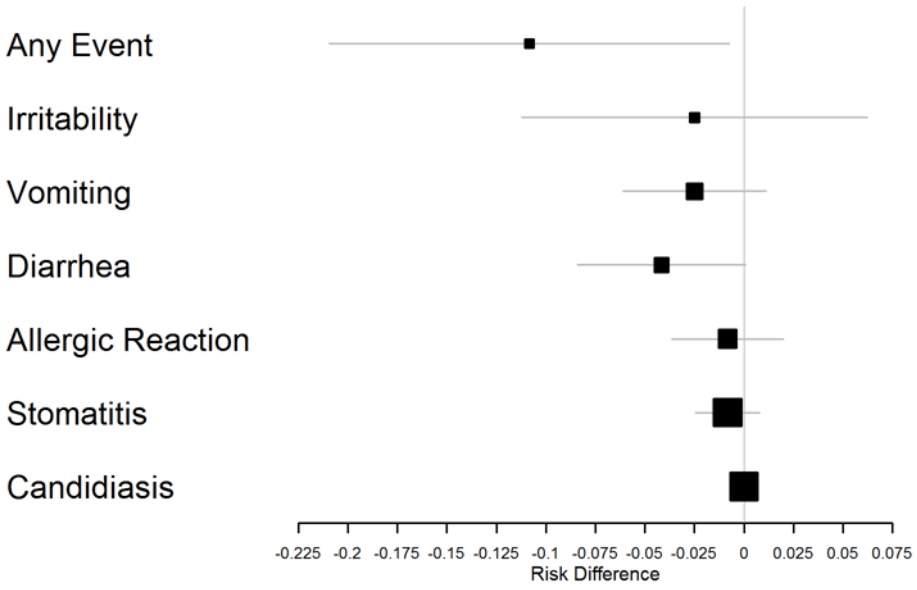
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 5: Forest Plot of Risk Difference of Solicited Events on Day 1-5 of Grade Severe - CC-V1 Population



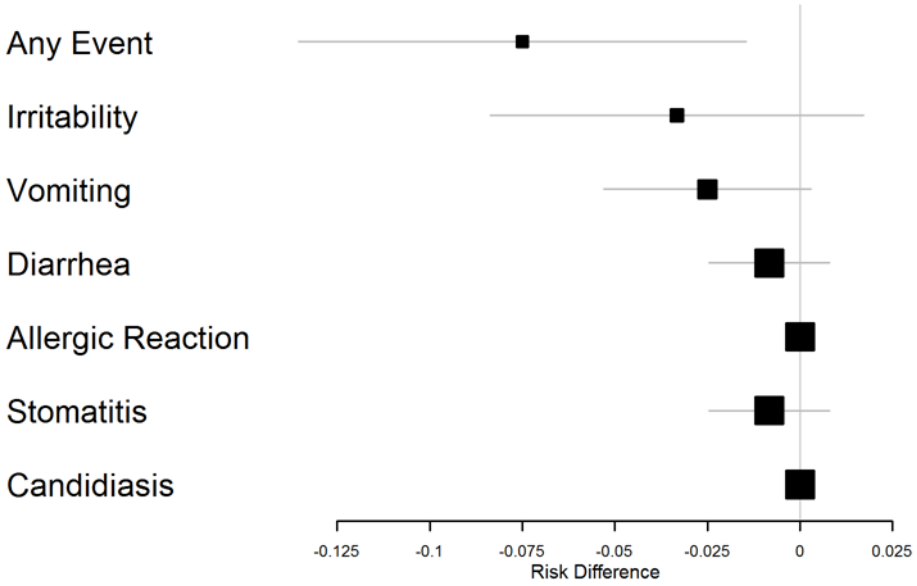
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 6: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Mild, Moderate, or Severe - CC-V2 Population



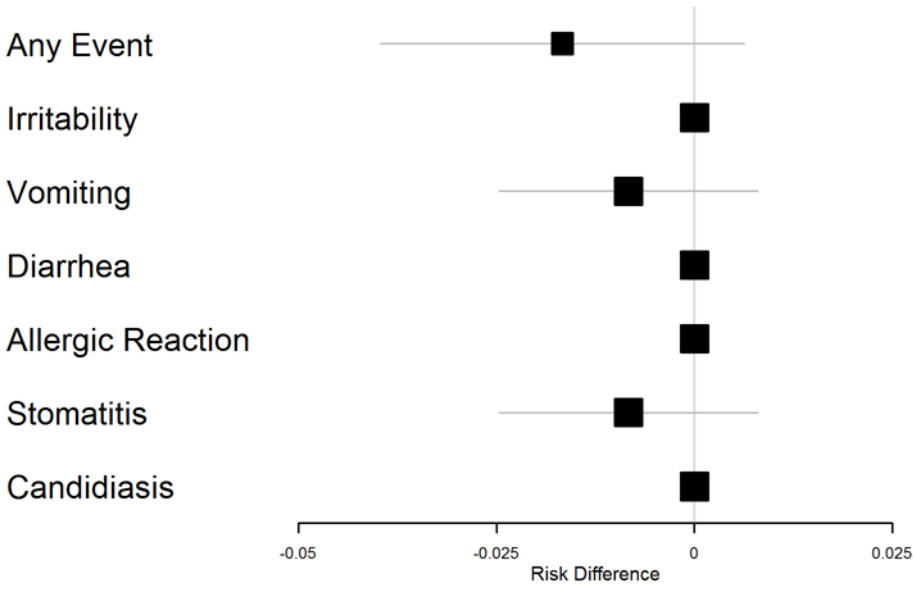
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 7: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Moderate or Severe - CC-V2 Population



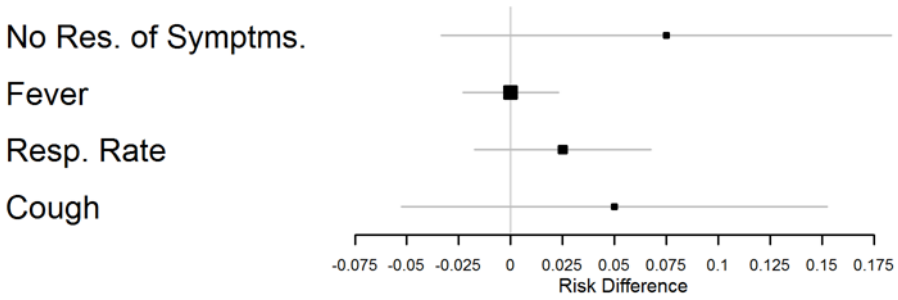
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 8: Forest Plot of Risk Difference of Solicited Events on Day 1-18 of Grade Severe - CC-V2 Population



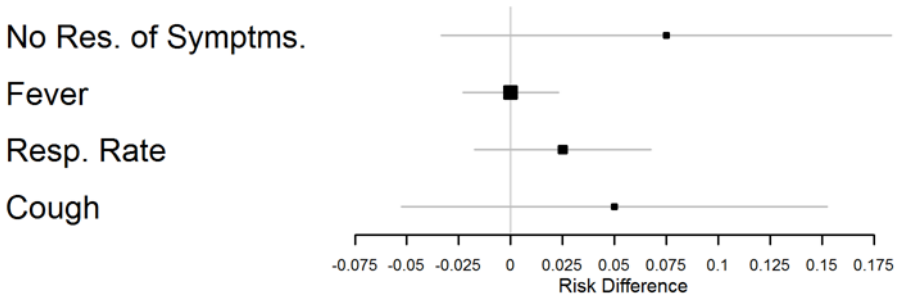
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 9: Forest Plot of Risk Difference of Lack of Resolution of Symptoms and Its Components - Outcome Assessment Visit #1 - CC-V1 Population



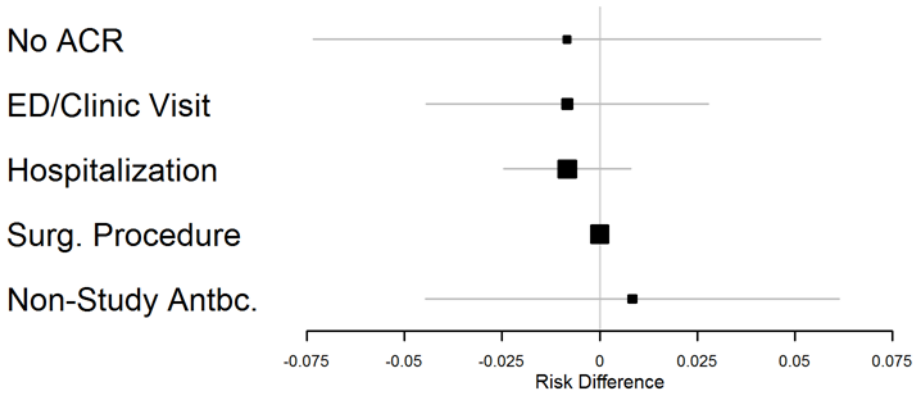
Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 10: Forest Plot of Risk Difference of Lack of Resolution of Symptoms and Its Components - Outcome Assessment Visit #2 - CC-V2 Population



Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 11: Forest Plot of Risk Difference of Lack of Adequate Clinical Response and Its Components - Outcome Assessment Visit #1 - CC-V1 Population

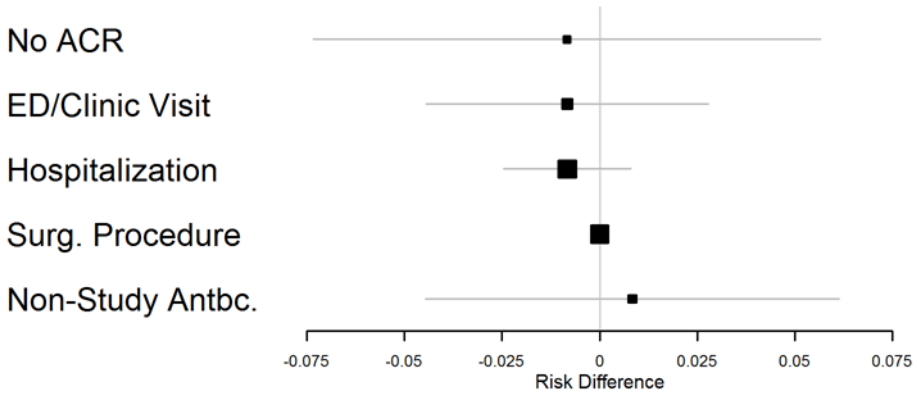


Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 12: Forest Plot of Risk Difference of Any Receipt of Non-Study Antibiotics or Medically Attended Visit - Outcome Assessment Visit #1 - CC-V1 Population

[Figure 12 will repeat Figure 11 without the No ACR confidence interval and will show confidence intervals for all events Day 1 – Day 5 (ED/Clinic Visit, Hospitalization, Surgical Procedure, and receipt of Non-Study Antibiotic) rather than only those satisfying the definition for lack of adequate clinical response.]

Figure 13: Forest Plot of Risk Difference of Lack of Adequate Clinical Response and Its Components - Outcome Assessment Visit #2 - CC-V2 Population

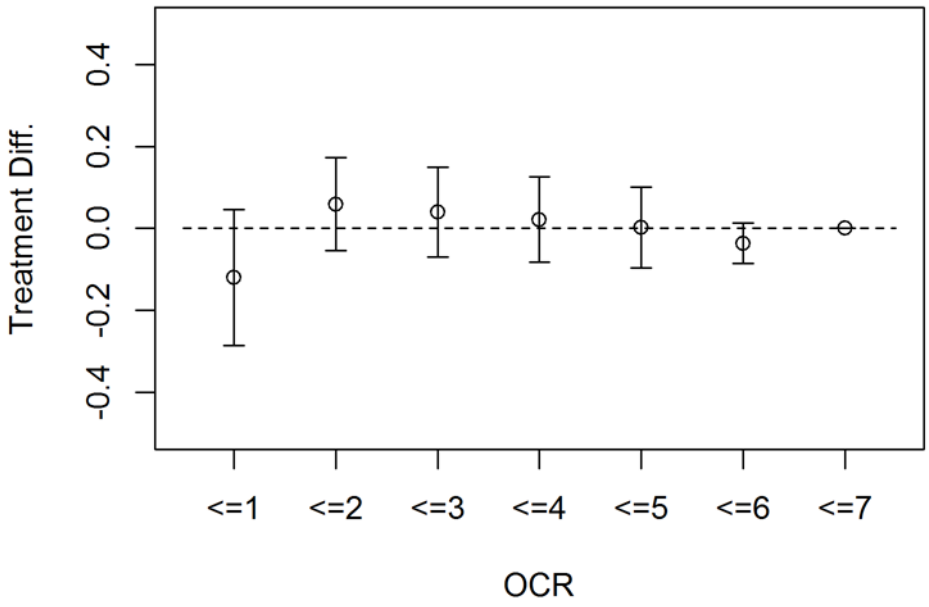


Note: Positive risk difference indicates a higher proportion of short-course subjects experienced the event than standard-course subjects.

Figure 14: Forest Plot of Risk Difference of Any Receipt of Non-Study Antibiotics or Medically Attended Visit - Outcome Assessment Visit #2 - CC-V2 Population

[Figure 14 will repeat Figure 13 without the No ACR confidence interval and will show confidence intervals for all events Day 1 – Day 18 (ED/Clinic Visit, Hospitalization, Surgical Procedure, and receipt of Non-Study Antibiotic) rather than only those satisfying the definition for lack of adequate clinical response.]

Figure 15: 95% Cumulative Difference Plot[1] of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - ITT Analysis



[1] Plots the 95% confidence intervals of the difference in the probability Pr(OCR≤k | treatment=m), where k=1,2,3,4,5,6,7 and m=0,1, between the two treatment groups. Note there can be no difference in Pr(OCR≤8 | treatment=m) since the probability is always 1 for each treatment arm, so only the first seven levels of the OCR are plotted.

Figures with similar format:

Figure 16: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - CC-V1 Analysis

Figure 17: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - ATP-V1 Analysis

Figure 18: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #1 - Worst Case Analysis

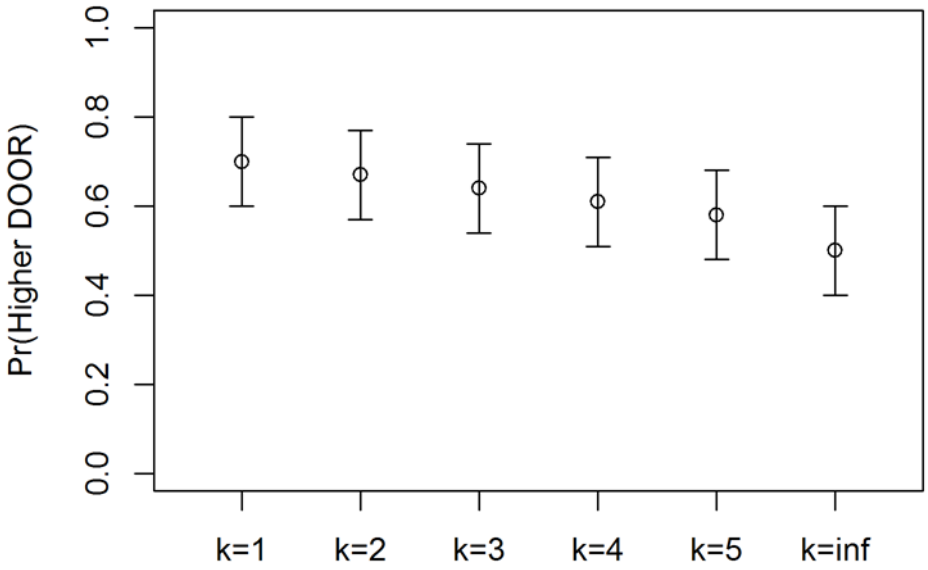
Figure 19: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - ITT Analysis

Figure 20: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - CC-V2 Analysis

Figure 21: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - ATP-V2 Analysis

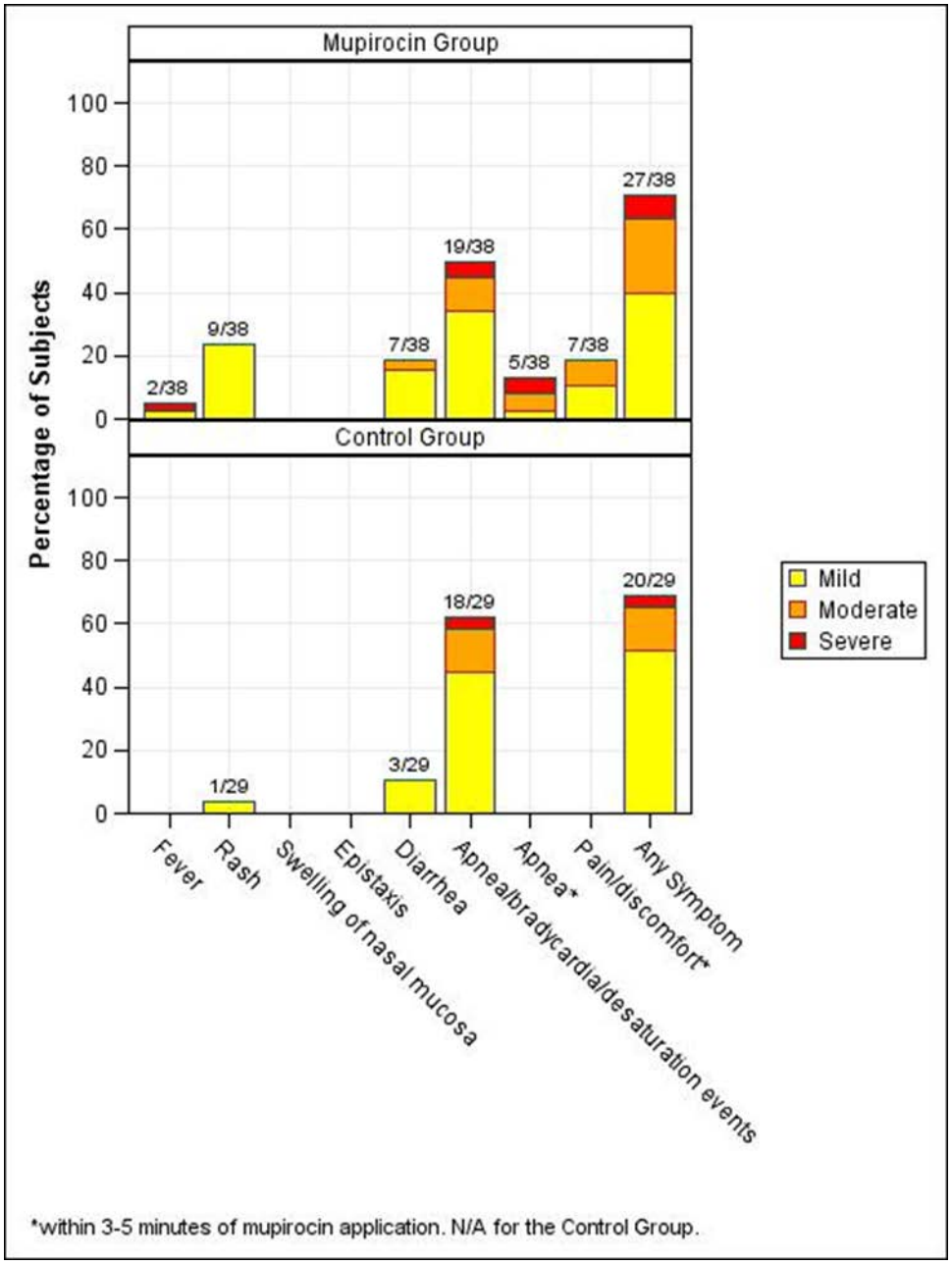
Figure 22: 95% Cumulative Difference Plot1 of Ordinal Clinical Response (OCR) by Treatment Arm - Outcome Assessment Visit #2 - Worst Case Analysis

Figure 23: C-V1 Evaluation of DOOR at Outcome Assessment Visit #1 - Minimum Required Difference in Days for Antibiotic Use "Tie-Breaking" Varies k=1,2,3,4,5, or Infinity



14.3.1.1 Solicited Adverse Events

Figure 24: Maximum Severity of Solicited Adverse Events (by Symptom)



[Programming Note: This figure will present maximum severity of solicited events separately by treatment group. The mockup is an example only. The actual figure will contain treatment groups and solicited events relevant to the 14-0079 protocol.]

14.3.5 Displays of Laboratory Results

Not applicable

APPENDIX 3. LISTINGS MOCK-UPS

LIST OF LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

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

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1 - Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 2: 16.2.2.1 - Subject-Specific Protocol Deviations

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

Listing 3: 16.2.2.2 - Non-Subject-Specific Protocol Deviations

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 4: 16.2.3 - Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., ITT, CC-V1, ATP-1]	[e.g., ITT, CC-V2, ATP-2]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

16.2.4 Demographic Data

Listing 5: 16.2.4.1 - Demographic Data

Treatment Group	Subject ID	Sex	Initial Antibiotic	Initial Site of Treatment	Age at Enrollment (months)	Ethnicity	Race

[Implementation Note: If a subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."]

Listing 6: 16.2.4.2 - Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

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

Listing 7: 16.2.5 - Treatment Compliance

Treatment Group	Subject ID	Dose(s) Missed	Extra Doses
		[1,2,3,4,5,6,7,8,9,10]	

16.2.6 Solicited Events

Listing 8: 16.2.6 - Solicited Events

Treatment Group	Subject ID	Study Day	Irritability	Vomiting	Diarrhea	Allergic Reaction	Stomatitis	Candidiasis

16.2.7 Serious Adverse Events

Listing 9: 16.2.7 - Serious Adverse Events

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

16.2.8 Vital Signs and Physical Exam Findings

Listing 10: 16.2.8.1 - Vital Signs

Treatment Group	Subject ID	Visit Number	Temperature (°F)	Respiration Rate (breaths/min)	Pulse (beats/min)

Listing 11: 16.2.8.2 - Physical Assessment Findings

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.9 Concomitant Medications

Listing 12: 16.2.9 - Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

16.2.10 Medically Attended Visits

Listing 13: 16.2.10.1 - Medically Attended Visits - Standard Course

Subject ID	Visit Study Day	Visit Type[1]	Antibiotic[1]	Surgery[1]	Hospitalization[1]	Hospital Admit Day	Hospital Discharge Day

[1]Asterisk indicates the visit, antibiotic, surgery, or hospitalization were due to pneumonia or a complication of pneumonia.

Listing 14: 16.2.10.2 - Medically Attended Visits - Short Course

Subject ID	Visit Study Day	Visit Type[1]	Antibiotic[1]	Surgery[1]	Hospitalization[1]	Hospital Admit Day	Hospital Discharge Day

[1]Asterisk indicates the visit, antibiotic, surgery, or hospitalization were due to pneumonia or a complication of pneumonia.

16.2.11 Cough

Listing 15: 16.2.11.1 - Cough - Standard Course

	Cough Severity by Study Day or Visit																										
Subject ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**OAV[1]#1**	**OAV[1]#2**	**ETV[2]**

[1] OAV = Outcome Assessment Visit
[2] ETV = Early Termination Visit

Listing 16: 16.2.11.2 - Cough - Short Course

	Cough Severity by Study Day or Visit																										
Subject ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**OAV[1]#1**	**OAV[1]#2**	**ETV[2]**

[1] OAV = Outcome Assessment Visit
[2] ETV = Early Termination Visit

16.2.12 Presence of Fever in Previous 24 Hours

Listing 17: 16.2.12.1 - Presence of Fever in Previous 24 Hours - Standard Course

Subject ID	Outcome Assessment Visit #1		Outcome Assessment Visit #2		Early Termination Visit	
	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]

[1] Recorded oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F)
[2] Fever attributed to a process unrelated to the prior diagnosis of pneumonia

[Programming Note: Listing programmed from ACRTEMP and ACRFEV only.]

Listing 18: 16.2.12.2 - Presence of Fever in Previous 24 Hours - Short Course

Subject ID	Outcome Assessment Visit #1		Outcome Assessment Visit #2		Early Termination Visit	
	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]	Fever[1]	Unrelated[2]

[1] Recorded oral, rectal, axillary, or tympanic temperature ≥38.3˚C (100.9˚F)
[2] Fever attributed to a process unrelated to the prior diagnosis of pneumonia

16.2.13 Ordinal Clinical Response and DOOR, According to CC-V1 and CC-V2 Analyses[1]

Listing 19: 16.2.13 - Ordinal Clinical Response and DOOR, According to CC-V1 and CC-V2 Analyses[1]

Subject ID	Treatment Group	Outcome Assessment Visit #1			Outcome Assessment Visit #2		
		Ordinal Clinical Response	Days of Antibiotic Use	DOOR	Ordinal Clinical Response	Days of Antibiotic Use	DOOR

[1] Ordinal Clinical Response, Days of Antibiotic Use, and DOOR at Outcome Assessment Visits #1 and #2 are only listed for subjects that had the respective Outcome Assessment Visit (no imputed values are shown).

APPENDIX 4. NCA TEMPLATE

See separate document, if applicable.