Best Pharmaceuticals for Children Act

STATISTICAL ANALYSIS PLAN

FOR

NICHD-2013-ABS01

Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections (SCAMP Trial)

Version 1.0

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ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BPCA	Best Pharmaceuticals for Children Act
BUN	Blood Urea Nitrogen
CL	Clearance
CI	Confidence Interval
CYP450	Cytochrome P450
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
DCC	Data Coordinating Center
FiO_2	Fraction of inspired oxygen
GA	Gestational Age
ICH	International Conference of Harmonization
I-FABP	Intestinal Fatty Acid-binding Protein
ITT	Intention-to-treat Population
IV	Intravenous
IVH	Intraventricular Hemorrhage
NEC	Necrotizing Enterocolitis
NICHD	National Institute of Child Health and Human Development
PD	Pharmacodynamic
PK	Pharmacokinetics
PMA	Postmenstrual Age
PNA	Postnatal Age
SAE	Serious Adverse Event
$T_{1/2}$	Half-life
V	Volume of Distribution

1 SYNOPSIS

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the Pediatric Trials Network protocol NICHD-2013-ABS01, "Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections" sponsored by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration, European Medical Agency, and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society, for statistical practice [3].

Analysis reports will analyze data by treatment regimen as specified in this SAP. These analyses are anticipated to be used in clinical study reports (CSRs) for metronidazole, clindamycin, and piperacillin-tazobactam. Additional analyses in participants with positive blood cultures for bactaremia may be performed as discussed in Section 7.6. These analyses may be used in additional CSRs, including possible CSRs or data reports that target participants who received study ampicillin.

The planned analyses identified in this SAP may also be included in regulatory submissions or manuscripts. Post-hoc exploratory or sensitivity analyses not identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, analysis performed will be clearly identified as such in the CSR.

The following documents were reviewed in preparation of this SAP:

a. Clinical Research Protocol (Version 4, issued September 24, 2015).

b. Data Collection forms (DCFs).

c. ICH Guidance on Statistical Principles for Clinical Trials (E9).

The clinical protocol, and other identified documents, should be referenced for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless needed to describe the planned analyses. This SAP will not be updated for revisions of the protocol unless substantial changes in the planned analyses are required. Minor changes to the planned analyses will be identified in the CSR.

Sections 2 to 6 of this SAP describe study design and analysis populations. Sections 7 to 12 describe analysis plans for safety and efficacy analyses. The PK analysis plan is attached as Appendix A.

1.1 Study Synopsis

Protocol Title	Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections

Current Protocol Version	Version 4.0, issued September 24, 2015
Phase	2/3
Products	Metronidazole, clindamycin, piperacillin-tazobactam
Objectives	Primary: Safety of drug regimens Secondary: • Efficacy of drug regimens including ampicillin, metronidazole, clindamycin, piperacillin-tazobactam, and gentamicin in infants with complicated intra-abdominal infections • Pharmacokinetics (PK) of ampicillin, metronidazole, clindamycin, and piperacillin-tazobactam in infants with complicated intra-abdominal infections • Biomarker association with disease severity and antibiotic exposure • Association between genetic polymorphisms in CYP450 enzymes and metronidazole and clindamycin exposure • Comparison of intestinal microbiota between treatment arms • Cerebrospinal fluid (CSF) PK of metronidazole, clindamycin, and piperacillin-tazobactam in infant
Study Design	Partially randomized, multicenter, open-label, safety study
Study Population	Infants with complicated intra-abdominal infections (Groups 1–4) or those with suspected or confirmed infections (Group 5)
Number of Participants	Up to 284 (N~70 in each Group 1–3, N~50 in Group 4, N~24 in Group 5)
Number of Sites	Approximately 60
Inclusion Criteria	1. Informed consent obtained 2. ≤33 weeks gestation at birth (Groups 1–3, 5) 3. ≥34 weeks gestation at birth (Groups 4 and 5) 4. Postnatal age (PNA) <121 days (Groups 1–5) 5. Sufficient venous access to permit study drug administration (Groups 1–5) 6. Presenting physical, radiological, and/or bacteriological findings of a complicated intra-abdominal infection within 48 hours prior to randomization/first study drug dose** (Groups 1- 4). Complicated intra-abdominal infections include secondary peritonitis, necrotizing enterocolitis (NEC) grade II or higher by Bell's criteria, Hirschsprung's disease with perforation, spontaneous intestinal perforation, meconium ileus with perforation, bowel obstruction with perforation, gastroschisis with necrosis and/or perforation, omphalocele with necrosis and/or perforation, neonatal appendicitis, intestinal pneumatosis or portal venous gas, free peritoneal air on abdominal radiographic examination, or abdominal abscess (Groups 1–4). 7. Suspected or confirmed infection for which the study drug may provide therapeutic benefit and planned CSF collection per standard of care (Group 5)

Exclusion Criteria*:

1. History of anaphylaxis in response to study drugs (Groups 1–5)
2. Serum creatinine >2 mg/dL within 48 hours on measurement prior to and closest to randomization or first study drug dose (Groups 1-5)**
3. Known ALT >250 U/L or AST >500 U/L on measurement closest to the time of randomization or first study drug dose (Groups 1-5)**
4. Any condition that, in the judgment of the investigator, precludes participation because it could affect participant safety (Groups 1–5)

*Does not apply for Group 5 participants receiving drug per standard of care.

**Criteria must be satisfied by randomization (randomized Groups 1-3) or first study drug dose (non-randomized Groups 1-3, Group 4 and Group 5), whichever comes first.

Dose Schedule

Group	Ampicillin	Gentamicin	Clindamycin	Metronidazole	Piperacillin-tazobactam
1	X	X		X	
2	X	X	X		
3		X			X
4				X	
5			X	X	X

Drug	PNA *Days*	GA *wks*	PMA *wks*	Loading dose *mg/kg*	Maintenance dose *mg/kg*	Dosing interval *h*
Ampicillin	≤7	≤34			50	12
	>7 – ≤28	≤34			75	12
	≤28	>34			50	8
	>28	ANY			50	8
Metronidazole			<34	15	7.5	12
			≥34 – ≤40	15	7.5	8
			>40	15	7.5	6
Clindamycin			≤32		5	8
			>32 – ≤40		7	8
			>40 – ≤60		9	8
Piperacillin-tazobactam*			≤30		100	8
			>30		80	6

GA, gestational age; PMA, postmenstrual age. * Dosing based on the piperacillin component.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

Safety of drug regimens (ampicillin, metronidazole, clindamycin, piperacillin-tazobactam, and gentamicin).

2.2 Secondary Objectives

- Efficacy of drug regimens including ampicillin, metronidazole, clindamycin, piperacillin-tazobactam, and gentamicin in infants with complicated intra-abdominal infections
- Pharmacokinetics (PK) of ampicillin, metronidazole, clindamycin, and piperacillin-tazobactam in infants with complicated intra-abdominal infections
- Biomarker association with disease severity and antibiotic exposure
- Association between genetic polymorphisms in CYP450 enzymes and metronidazole and clindamycin exposure
- Comparison of intestinal microbiota between treatment arms
- Cerebrospinal fluid (CSF) PK of metronidazole, clindamycin, and piperacillin-tazobactam in infants

2.3 Primary Endpoint

The primary safety endpoint is mortality. In the primary analysis, mortality will be estimated within each treatment group.

2.4 Secondary Safety Endpoints

Key secondary safety endpoints are the occurrence of adverse events (AEs), serious adverse events (SAEs), and the outcomes of special interest (OSIs) listed in Section 10.3. Additional safety endpoints are clinical laboratory values.

2.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the clinical cure score, overall therapeutic success, and time to first full enteral feed.

2.6 Additional Endpoints

2.6.1 PK Endpoints

a. Clearance (CL)
b. Volume of distribution (V)

2.6.2 Biomarker Endpoints

a. Urine I-FABP/creatinine concentrations

3 STUDY METHODS

3.1 Overall Study Design and Plan

This is a phase 2/3, prospective, open-label, partially randomized, multicenter, safety trial. The study is designed to evaluate the safety of 3 therapeutic regimens in premature infants (≤33 weeks GA) and 1 therapeutic regimen in late preterm and term infants (≥34 weeks GA) with complicated intra-abdominal infections. This study will also evaluate the CSF PK of metronidazole, clindamycin, and piperacillin-tazobactam in infants with suspected or confirmed infections.

3.2 Selection of Study Population

3.2.1 Premature Infants (Groups 1–3)

Up to 210 premature infants (≤33 weeks gestation at birth) will be assigned to the following drug regimen groups:

Group 1 (N ~70): ampicillin, gentamicin, and metronidazole
Group 2 (N ~70): ampicillin, gentamicin, and clindamycin
Group 3 (N ~70): piperacillin-tazobactam and gentamicin

At least 40 participants will be assigned to each group by randomization. Participants who meet eligibility criteria for the study and have been prescribed all drugs in one of the study drug regimens per standard of care prior to study entry can be enrolled and assigned to the corresponding group without randomization.

3.2.2 Late Preterm and Term Infants (Group 4)

Approximately 50 late preterm and term infants (≥34 weeks gestation at birth) will be assigned to Group 4. Infants assigned to Group 4 will receive metronidazole in addition to the antibiotic regimens prescribed per standard of care.

Group	Initial regimen	Anaerobic coverage
4	Per standard of care	Metronidazole

3.2.3 Infants Undergoing CSF Collection (Group 5)

Approximately 24 infants with suspected or confirmed infection for which the study drug may provide therapeutic benefit in whom CSF is planned to be collected per standard of care will be assigned to Group 5. Infants in Group 5 will be assigned by the site principal investigator to subgroup(s) (a, b, c) and receive up to 10 days of dosing of study drug. Infants assigned to Group 5 will receive study drug as part of or in addition to the antibiotic regimens prescribed per standard of care.

Group 5a (N~8): metronidazole
Group 5b (N~8): clindamycin
Group 5c (N~8): piperacillin-tazobactam

Participants in Groups 1-4 can be co-enrolled into Group 5.

3.3 Method of Treatment Assignment and Randomization

3.3.1 Premature Infants (Groups 1–3)

For randomized participants ≤33 weeks gestation at birth, the participant number and the randomized treatment will be obtained through the AdvantageEDC enrollment module. In the event that AdvantageEDC is not available at the time of randomization, a back-up randomization procedure will be used. If a participant is randomized but does not receive a dose of any study drug, that participant will not count towards total sample size and will be replaced by a new participant who, in turn, will be assigned a new identification number. Eligible

participants will be randomly assigned to the 3 drug regimen groups (Groups 1–3) using a 1:1:1 allocation ratio. Randomization will be stratified by site. The permuted block design of random block sizes will be used to ensure group balance of randomized drug group within each block.

A randomization scheme that will allow continued enrollment during times of drug shortages will be implemented. In instances of a drug shortage, when a site either restricts the use of, or does not have one of the following study drugs (metronidazole, clindamycin or piperacillin-tazobactam) subjects at the site will be randomized at a 1:1 ratio to one of the unaffected study Groups or assigned to the unaffected study group if 2 drugs are unavailable. The original 1:1:1 randomization plan will be re-instituted once the drug shortage at the site is over.

Non-randomized participants will be assigned to treatment groups as discussed in Section 3.2.1. Dose amounts for participants enrolled in Groups 1-3 who are not randomized must be adjusted to protocol dosing unless the total daily dose for each antibiotic (excluding aminoglycosides) administered per standard of care is equal or greater to the protocol specified drug dose amount.

3.3.2 Late Preterm and Term Infants (Group 4)

Eligible late preterm and term infants will be enrolled into Group 4 as discussed in Section 3.2.2.

3.3.3 Infants Undergoing CSF Collection (Group 5)

Assignment to subgroups will be at the discretion of the treating physician or determined centrally by the study team based on real-time monitoring of enrollment considering number of infants enrolled in each group. If infants are receiving study drugs as standard of care prior to consent, drug administration can continue at the same doses. If study drug is added to the standard-of-care regimen, doses specified in the protocol should be used.

4 ANALYSES AND REPORTING

4.1 Interim Analyses

No interim analyses are scheduled.

4.2 Final Analysis

All final, planned analyses identified in this SAP will be performed only after the last participant has completed the last study visit and end of study assessments, and all relevant study data have been processed and integrated into the analysis database and all relevant data queries have been resolved. In addition, no database will be locked or final analyses completed until this SAP has been approved.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

5 SAMPLE SIZE DETERMINATION

The study is powered to estimate the incidence of death within 30 days for each drug regimen (Groups 1 to 3). The incidence of death in this population is expected to be 20%. A sample size of 70 will allow us to estimate the 20% death rate with a 95% confidence interval (CI) that has a precision (half- width) of 10% (95% CI: 11.4%, 31.3%).

6 ANALYSIS POPULATIONS

6.1 ITT Population

Participants who receive at least 1 dose of any study drug in the randomized or assigned protocol treatment group will be included in the intention-to-treat (ITT) population used for the safety (Groups 1–5) and efficacy analyses (Groups 1–4). In ITT analyses, participant treatment assignments will be based on the original randomization regardless of changes to the treatment regimen. The Groups 1 to 3 full (randomized and non-randomized) ITT population will be separated into randomized and non-randomized ITT populations for select analyses as specified in Section 7.2. The full ITT population will be used in the primary safety analysis (Section 10.1).

6.2 Per Protocol Population

Select secondary safety and efficacy analyses in Groups 1 to 4 will also be conducted based on the final group assignment (per protocol population). Participants will be eligible for the per protocol population if they received at least 1 study dose of each study drug in the randomized or assigned protocol treatment group. Participants with protocol deviations for dose amount or duration of IV infusion will be eligible for this population. Since only 1 valid study dose is required for inclusion in the per protocol population, dose frequency deviations will not affect inclusion in this population. Participants who are lost to follow-up before 30 days will still be eligible for this population. The Groups 1 to 3 full (randomized and non-randomized) per-protocol population will be separated into randomized and, if different from the non-randomized ITT population, non-randomized per protocol populations for select analyses as specified in Section 7.2. As discussed in Section 7.3, if not sufficiently different from the ITT population, the per protocol population will not be analyzed separately in the CSR.

6.3 PK Analysis Population

Infants in any group with at least 1 evaluable PK sample will be included in the PK analysis population.

7 GENERAL ISSUES FOR STATISTICAL ANALYSIS

Data will be summarized by treatment group. Study disposition and demographic characteristics will also be summarized across all treatment groups. Safety and efficacy variables will only be cumulatively summarized across Groups 1 to 3 with Groups 4 and 5 summarized separately. For continuous variables, descriptive statistics will include number of observations, mean, standard deviation, median, minimum, and maximum. Discrete variable summaries will include frequencies and percentages. Categories of AEs, protocol deviations, and medical history events will be summarized by the number of events and number of participants with the event.

Event rates will primarily be estimated within each treatment group. Confidence intervals will be estimated or hypothesis testing performed for select endpoints as described in Sections 9 and 10. Confidence intervals will be calculated using the 95% confidence level. Hypothesis tests will be performed at the α=0.05 significance level. Since primary and secondary analyses are primarily descriptive in nature, adjustments for multiplicity are not planned. Confidence intervals for event rates and pairwise differences between treatment groups will be calculated using Wilson score confidence intervals [4]. P-values for comparing overall treatment differences between Groups 1 to 3 will be calculated using the Fisher's exact test. No statistical comparisons are anticipated between Groups 1 to 3 and Groups 4 or 5.

Planned analyses for Section 14 tables, listings, and figures are anticipated to be performed using version 9.3 or higher of the SAS Software except variable selection for logistic regression models is expected to be performed in the GLMNET library of the R software package [5]. Additional secondary and exploratory analyses may be performed in different software packages that will be specified in the CSR. Population PK analyses, which will include analyses of the association between genetic polymorphisms in CYP450 enzymes and metronidazole and clindamycin exposure, are discussed in Appendix A.

7.1 Handling of Multiple Enrollments and Non-Enrollments

Participants who enroll in Group 5 while in the study for Groups 1 to 4 will be excluded from the Group 5 safety population to prevent including redundant safety data in multiple populations. Therefore, data from these participants will only be included in the Groups 1 to 4 safety summaries.

Participants who enroll in Group 5 after completion or early termination for the original Groups 1 to 4 enrollment will be included in the Group 5 safety population. Data from the Group 5 enrollment period will only be included in Group 5 safety summaries. Data from the Groups 1 to 4 enrollment period will only be included in the Groups 1 to 4 safety summaries.

Participants who are not enrolled in the study but do have research (not standard of care) clinical laboratory samples collected at baseline will be followed for safety related to study procedures. These participants will be included in the summary of study disposition (Section 8.1) and participant listings.

7.2 Analysis Populations for Randomized and Non-randomized Groups 1 to 3 Participants

All analyses will be performed using the full (randomized and non-randomized) analysis populations. Additional summaries will be presented for select endpoints using separate randomized and non-randomized populations. These endpoints are:

- Overall therapeutic success rate (Section 9.2)
- Mortality and other OSI rates (Sections 10.1 and 10.3)
- AE, SAE, and related AE rates (Section 10.2)

7.3 Per Protocol Analysis Population: Endpoints for Analysis and Criteria for Deletion

All endpoints will be analyzed and all baseline summaries will be performed using the ITT population. The following endpoints will be analyzed using the per protocol population as a secondary sensitivity analysis:

- Overall therapeutic success rate (Section 9.2)
- Mortality and other OSI rates (Sections 10.1 and 10.3)
- AE, SAE, and related AE rates (Section 10.2)

Additionally, as shown in Section 12, a subset of demographic and baseline summaries will be presented using the per protocol population.

It is anticipated that few participants will either complete the study without receiving the full study regimen or have sufficient protocol deviations to be excluded from the per protocol population. If the sample sizes in the ITT and per protocol populations differ by < 10% in each of the randomized groups, the secondary safety and efficacy analyses using the per protocol population will not be performed.

7.4 Logistic Regression Modeling and Covariate Adjustment

Since participant characteristics may differ greatly between randomized and non-randomized Groups 1 to 3 participants, a secondary sensitivity analysis will be performed to estimate event rates for key safety (mortality and other OSI as described in Sections 10.1 and 10.3) and efficacy endpoints (overall therapeutic success as described in Section 9.2) adjusted for randomization group and other covariates that may differ between randomization groups. Since endpoints are binary, logistic regression will be used. Due to low sample sizes and low expected event rates, this sensitivity analysis will only performed for events with event rates ≥ 15% (≥ 10 of 70 planned participants) in any of the three treatment groups.

The following variables will be considered for the model:

- Treatment group
- Randomization group (randomized or non-randomized)
- Demographic variables (listed in Section 8.4)
- Baseline measures: length, actual weight, serum creatinine, and urinary intestinal fatty acid binding protein (I-FABP)/creatinine ratio
- Baseline gastrointestinal disorder derived from medical history: whether the patient was diagnosed with necrotizing enterocolitis (NEC); presence of a surgical condition (laparotomy, peritoneal drain replacement, intestinal resection, ostomy placement); presence of intestinal strictures, intestinal perforation, or short bowel syndrome

Variable selection for the final model will be performed using least absolute shrinkage and selection operator (LASSO) regression.

7.5 Selection of Baseline Measurements

Baseline measurements will be defined as measurements before (or at the exact time of) the first dose of study treatment. Participants may have previously received treatment regimen drugs per standard of care before the collection of study baseline data. For measurements such as weight and length in which collection time will not be recorded, data collected on the day of study treatment initiation will be used as baseline measurements.

7.6 Analysis of Participants with Positive Cultures

The number of participants with positive blood cultures will be identified by treatment regimen. If positive blood cultures are reported in a sufficient number of Groups 1 to 3 participants, additional analyses of these participants will be performed. Key safety (AE and OSI) and efficacy endpoints will be reported in these participants with positive blood cultures. Analyses will be performed by study drug in addition to regimen. All participants who received ampicillin in the ITT population across Groups 1 and 2 would be classified into one group for analyses by study drug.

8 STUDY PATIENTS, DEMOGRAPHICS, AND DOSING

8.1 Disposition of Participants and Withdrawals

A summary of participant accounting and final study disposition will be provided. The number of Groups 1 to 4 participants who were lost to follow-up before 30 days post-therapy will be summarized along with reasons for discontinuation. For participants who discontinued at any point of the study, the primary reason for discontinuation will be summarized. A breakdown of enrollment in the ITT and per protocol populations by study site will also be provided. In Group 5, enrollment will be summarized by drug (metronidazole, clindamycin, or piperacillin-tazobactam).

8.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for each participant will be summarized in a data listing.

8.3 Protocol Violations and Deviations

All protocol deviations will be reported by site and category of deviation. Deviations due to incorrect dosing will be summarized. A detailed listing of all protocol deviations by participant will be included.

8.4 Demographics and Other Baseline Characteristics

Demographic variables will include gender, postnatal age (PNA) at first study dose, post-menstrual age (PMA) at first study dose, gestational age (GA), birth weight, race, and ethnicity. Baseline measures of length and actual weight will also be summarized.

Medical history will be Medical Dictionary of Regulatory Affairs (MedDRA) coded and summarized by system organ class and preferred term. Terms that have been MedDRA-coded as both with and without a “neonatal” specification will be reported without neonatal being specified; for example, terms coded as “NEC” and “NEC neonatal” will be summarized together under the “NEC” preferred term. Medical history will also be summarized in a participant listing which will include the actual reported medical conditions. Also listed will be system organ class, preferred term, onset date, current status, and resolution date (if applicable).

Data listings of baseline physical examination results will be prepared. Post-treatment physical examination results will not be collected. Additional baseline measures (microbiology cultures, prior medications, and clinical laboratory values) will be summarized as discussed in Section 10.

8.5 Dosing

The dosing summary will include days of study dosing, the number of study doses, mean administered mg/kg dose, and maximum administered mg/kg/day dose per participant for each drug in the treatment regimen. The administration of study drugs that are not part of the treatment regimen will be summarized as prior or concomitant medications. In the CSR, dosing will be summarized in Section 12 text and tables.

8.6 PK Sampling

Inclusion in the PK population will be summarized as described in Section 8.1. PK sample collection will be discussed as part of the PK analysis summary (Appendix A).

9 EFFICACY ANALYSIS

Efficacy is a secondary study objective and will be assessed by group in Groups 1 to 4. Formal comparisons will not be made between treatment groups. All efficacy analyses will be performed using the full ITT population unless otherwise noted. The evaluation of efficacy will be based on the following:

- Overall therapeutic success (including the clinical cure score)
- The time to first full enteral feed (gastrointestinal endpoint)

9.1 Clinical Cure Score

The clinical cure score will primarily be used to evaluate therapeutic success (Section 9.2). The cure score will be calculated using data up the end of therapy visit and up to 30 days after the last dose of study drug. The cure score will be collected upon study termination in participants who terminate before 30 days. The elements of the presumptive clinical score are listed below.

1. Fraction of inspired oxygen (FiO_2)
2. Urine output
3. Cardiovascular inotrope support
4. Need for mechanical ventilation
5. Presence of seizure
6. Lowest serum pH

Scoring is defined in Table 1. Participants identified by the treating site as having normal urine output will be assigned scores of 1 for the urine output component of the score when the exact output is mL/kg/h is not collected. Participants on room air will be assigned scores of 1 for the FiO_2 component of the cure score. Participants with known urine output or FiO_2 at the immediate post-treatment time point but unreported data at the 30 day output will have the 30 day output imputed using last observation carried forward. Participants with unknown values at both visits will be assigned a score of 0 for this component of the cure score. Other elements of the cure score are not anticipated to be missing in participants with an evaluable cure score.

The cure score will be missing in participants who die before the cure score can be assessed.

Table 1. Elements of the clinical cure score

Element	Score
FiO_2 ≤ baseline FiO_2	1
Urine output ≥1 mL/kg/h for 24-hour period prior to assessment	1
Absence of inotropic support at time of assessment	1
Absence of mechanical ventilation at time of assessment	1
No seizure in 24-hour period prior to assessment	1
pH ≥7.25 or not measured in 24 hours prior to assessment	1

The cure score will be summarized by post-treatment time point using summary statistics. Components of the cure score will be summarized at baseline and at each post-treatment time point.

9.2 Overall Therapeutic Success

Success will be defined as all of the following:

- Alive at 30 days post-treatment
- Negative bacterial blood cultures
- 30-day clinical cure score >4

Failure will be defined by any of the following:

- Death through 30 days post-treatment
- Positive bacterial blood cultures
- 30-day clinical cure score ≤4

The closest blood culture result at or prior to the 30-day assessment will be used to assess overall therapeutic success.

In participants who early terminate, determination of success will use data until early termination. As a separate sensitivity analysis, success rates will be summarized by whether the participant (A) early terminated for reasons other than death or (B) either died or had data collected to the end of the 30-day follow-up period.

9.3 Gastrointestinal Endpoint

The time to first full enteral feed (≥100 mL/kg/day) will be calculated as the number of days from the day of the start of study drug to the day of the first full enteral feed after the start of study. Summary statistics for time to first feed will be calculated using participants with full feeds before the end of study follow-up. Kaplan-Meier plots will be created for time to feed. Participants who died or were lost to follow-up before the first full feed will be treated as censored observations at the day of death or last follow-up. Kaplan-Meier estimates for the proportion of participants with full feed as of 30 or 90 days post-treatment will be calculated.

10 SAFETY AND BIOMARKER ANALYSIS

The evaluation of safety will be based upon the following:

- Deaths
- AEs and SAEs
- OSIs

- Clinical laboratory values
- Intestinal microbiota
- Microbiology cultures
- Concomitant medications

All safety measures and the urine I-FABP/creatinine biomarker will be evaluated in Groups 1 to 4. Only AEs, SAEs, clinical laboratory values, microbiology cultures, and concomitant medications will be collected and evaluated in Group 5 participants. All safety analyses in Group 5 will be summarized using only the ITT population (Section 6.2).

10.1 Deaths

The proportion of participants who died within 30 days estimated within each treatment group will be the primary safety endpoint for Groups 1 to 3. The full ITT population will be the used for the primary analysis. Mortality will be analyzed as discussed for OSIs in Section 10.3.

10.2 Adverse Events and Serious Adverse Events

An **adverse event or adverse drug reaction** is any untoward medical occurrence in humans, whether or not considered drug related which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator is considered an AE.

A **suspected adverse reaction** is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A reasonable possibility implies that there is evidence that the drug caused the event.

An **adverse reaction** is any AE caused by the drug.

A **serious adverse event (SAE)** or **serious suspected adverse reaction** or **serious adverse reaction** as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

1. Death
2. Life-threatening AE (“life-threatening” means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

The **severity** of an adverse event is determined by the investigator, who should use the following definitions when assessing the intensity of an adverse event:

1. MILD: Participant is aware of symptoms or has minor findings but tolerates them well and no or minimal intervention required

2. MODERATE: Participant experiences enough symptoms or findings to require intervention
3. SEVERE: Participant experiences symptoms or findings that require significant intervention

OSIs that are reported as AEs or SAEs as discussed in Section 10.3 will be included in the summaries for both AEs or SAEs and OSIs. All AEs, including suspected adverse reactions, and SAEs will be MedDRA coded and summarized for the following endpoints:

1. The total number of AEs and SAEs experienced
2. The number and percentage of subjects who experienced at least one AE and number who experienced at least one SAE
3. The number and percentage of AEs and SAEs at each level of severity (mild/moderate/severe)
4. The number and percentage of participants by the greatest severity of AE and SAE experienced
5. The number and percentage of AEs and SAEs by relationship to study treatment.
6. The number and percentage of participants by the strongest relationship to study medication of AE and SAE experienced.
7. The number and percentage of AEs and SAEs by relationship to study treatment and severity.
8. The number and percentage of participants who experienced AEs or SAEs by MedDRA system organ class and preferred term.
9. The number and percentage of participants who experienced AEs or SAEs by MedDRA system organ class, preferred term, and severity level.
10. The number and percentage of participants who experienced AEs or SAEs by MedDRA system organ class, preferred term, and relationship to study medication.

10.3 Outcomes of Special Interest

OSI are:

1. Gastrointestinal (GI) surgeries
2. Progression to a higher stage of NEC, if NEC is the cause of the complicated intra-abdominal infection
3. Intestinal strictures
4. Intestinal perforation
5. Positive blood culture (bacterial or fungal)
6. Short bowel syndrome
7. Seizures
8. Death
9. Intraventricular hemorrhage (IVH) grade 3 or 4
10. Feeding Intolerance

Definitions of qualifying events are summarized in the study protocol. For participants enrolled under protocol version 3.0 or later, events that are study drug regimen-related will be reported separately as AEs or SAEs if they occur within the AE or SAE reporting window. As specified in the study protocol, a blinded adjudication committee will review data at the end of the study to determine: 1) presence of intestinal strictures, intestinal perforation, short bowel syndrome and 2) cause of mortality. If there are discrepancies between the data entered by the site and the

determination of the adjudication committee, the adjudication committee's determination of these events will be used in the Section 14 table summaries of OSI. Discrepancies will be summarized in the text of the final data report.

Positive blood cultures will be counted as OSI if reported as positive after the first day of study dosing and either no baseline blood culture was reported or the previous baseline blood culture was negative. Other events will be reported as OSI if they occur after the start of study dosing.

For each OSI, confidence intervals will be calculated for the proportion of the treatment group who experience the OSI. The Fisher's exact test will be used to compare outcomes of special interest between Groups 1-3. Pairwise differences between Groups 1 to 3 will be calculated with corresponding Bonferroni-adjusted confidence intervals if significant differences are found between treatment groups for the primary outcome of death.

10.4 Clinical Laboratory Evaluations

The following clinical laboratory values will be summarized:

1. Albumin
2. ALT
3. AST
4. Direct bilirubin
5. Blood urea nitrogen (BUN)
6. Creatinine
7. Potassium
8. Sodium

For clinical laboratory values, change from baseline, percentage change from baseline, and shift in clinical assessment will be assessed using

1. The closest post-dose value collected on or before the last day of dosing
2. The last collected value during the day 1 to 3 post-therapy follow-up.

Improvement or worsening of the clinical assessment from normal, not clinically significant abnormal, or clinically significant abnormal will be used to summarize shifts in assessment. If multiple pre-dose measurements are available, the baseline value will be the closest measurement obtained before first study dose. The closest measurement prior to both post-treatment time points will be used in the analysis. All clinical laboratory values will be summarized in the data listings. Clinically significant values identified by the study sites will be flagged.

10.5 Intestinal Microbiota

Intestinal microbiota will be evaluated from stool samples that are scheduled to be collected at baseline and during and after treatment. The lack of collection of stool samples are not a protocol deviation, and samples at each scheduled time point are not expected in all participants. Profiles of intestinal microbiota will be described including the number and types of microorganisms. These profiles will be compared between treatment arms. Analyses will be summarized in a separate report and are not included in the CSR Section 14 tables listed in Section 12.

10.6 Microbiology Cultures

Microbiology culture will be summarized by participant using the following endpoints: participants with positive cultures, participants with positive cultures by type of specimen, and participants with positive cultures by finding. These endpoints will be summarized at baseline, at treatment discontinuation, and through 30 and 90 days post-treatment. The baseline summary will include all baseline findings. Post-treatment time points will use the most recent culture prior to the time point for each type of collected specimen. Additionally, whether any post-treatment positive bacterial or fungal blood culture was collected will be summarized as part of the OSI analysis (Section 10.3). All collected cultures will be presented in the data listings.

10.7 Prior and Concomitant Medications

All medications will be coded using the WHO drug classification system. Concomitant medications will be defined as medications with the first reported dose after the first study dose. Prior medications will be defined as medications administered before the first study dose. This will include prior medications that participants continued on after the start of study treatment. Prior and concomitant medications will be summarized separately.

Frequency distributions of medications will be listed by drug classification and drug name. A listing of medications by participant will include start and end dates (or ongoing). The number of days on either any antibiotics or antibiotics contained in the study treatment regimen before or after the start of study dosing will be summarized.

10.8 Participant Profile Plots

Participant profile plots will be generated to summarize dosing and safety events over the course of the study. These plots will include the days of the end of study treatment; the days of the start and end of antibiotic treatment taken as a concomitant medication; days in which OSIs are reported; days in which SAEs are reported; days in which AEs are reported; and positive microbiology culture results. Day 1 for the profile plots will be defined as the first day of treatment. Plots will only be generated for participants with OSIs or SAEs.

10.9 Urine I-FABP/Creatinine Biomarker Analysis

Statistical correlation methodologies will be used in an exploratory analysis to characterize the association between urinary intestinal fatty acid binding protein (I-FABP)/creatinine concentrations and both OSI occurrence and antibiotic exposure. Logistic regression will be used to predict OSI occurrence using I-FABP/creatinine ratio at baseline adjusted for other variables as discussed in Section 7.5. The relationship between I-FABP/creatinine concentrations and exposure will be evaluated using estimates of exposure from the population PK model (Appendix A).

Additionally, a t-test or nonparametric signed-rank test will be used to compare the last evaluated pre-event I-FABP/creatinine ratio in participants with and without GI OSIs. A regression analysis will be performed to describe the time course of the ratio up to the time of the OSI adjusted for baseline conditions.

11 REFERENCES

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[4] Brown LD, Cai TT, DasGupta A (2001). Interval Estimation for a Binomial Proportion. *Statistical Science.* 16(2), 101-133.

[5] Friedman J, Hastie T, Tibshirani R (2010). Regularization Paths for Generalized Linear Models via Coordinate Descent. Journal of Statistical Software, 33(1), 1-22.

12 TABLES, LISTINGS, AND FIGURES

Main Table Number	Table Number and Population	Table Title / Summary	Supporting Listing Number
14.1 STUDY DISPOSITION, STUDY CONDUCT, AND BASELINE			
14.1.1.1	All Participants	Participant Accounting and Study Disposition by Treatment Group	16.2.1
14.1.1.2	Full ITT	Participant Enrollment by Site and Treatment Group	16.2.1
14.1.2	.1.1 ITT Groups 1 – 3 .1.2 ITT Groups 4 – 5 and Overall .2 Per Protocol	Demographic and Baseline Summary by Treatment Group a	16.2.3
14.1.3	.1.1 ITT Groups 1 – 3 .1.2 ITT Groups 4 – 5	Summary of Medical History by System Organ Class, Preferred Term and by Treatment Group	16.2.4
14.1.4	Full ITT	Summary of Prior Medications by Drug Classification, Drug Name and Treatment Group	16.2.7
14.1.5.1	All Participants	Protocol Deviation Classification by Site	16.2.6.1
14.1.5.2	All Participants	Protocol Deviation Classification by Reason for Deviation	16.2.6.1
14.1.5.3	All Sites	Summary of Site-Specific Protocol Deviations	16.2.6.2
14.2 EFFICACY			
14.2.1	Full ITT	Summary of the Clinical Cure Score by Treatment Group	16.2.14
14.2.2	.1 ITT .2 Per Protocol	Summary of Overall Therapeutic Success	16.2.14
14.2.3	Full ITT	Summary of the Time to First Full Enteral Feed by Treatment Group	16.2.10.2
14.3 SAFETY			
14.3.1.1	.1.1 ITT Groups 1 – 3	Summary of Adverse Events by Treatment Group	16.2.9.1,

	.1.2 ITT Groups 4 – 5 .2 Per Protocol		16.2.9.2
14.3.1.2	Full ITT	Summary of Adverse Events by Severity and by Relationship to Study Treatment	
14.3.1.3	Full ITT	Adverse Events by System Organ Class, Preferred Term and by Treatment Group	16.2.9.1
14.3.1.4	Full ITT	Serious Adverse Events by System Organ Class, Preferred Term and by Treatment Group	16.2.9.2
14.3.1.5	Full ITT	Adverse Events by System Organ Class, Preferred Term, Relationship to Study Treatment and by Treatment Group	16.2.9.1
14.3.1.6	Full ITT	Adverse Events Listed by Most Frequent Preferred Term and by Treatment Group	16.2.9.1
14.3.2	.1.1 ITT Groups 1 – 3 .1.2 ITT Group 4 .2 Per Protocol	Outcomes of Special Interest by Treatment Group	16.2.10.1
14.3.3	Full ITT	Summary of Clinical Laboratory Measurements by Treatment Group	16.2.11
14.3.4	Full ITT	Summary of Microbiology Cultures by Treatment Group	16.2.12
14.3.5	Full ITT	Summary of Concomitant Medications by Drug Classification, Drug Name and Treatment Group	16.2.7
14.3.6	Full ITT	Urine I-FABP/Creatinine Biomarker Analysis by Treatment Group	16.2.13

Figure Number	Population	Table Title / Summary
14.1	Full ITT	Participant Profile Plots

Listing Number	Population	Listing Title / Summary	Supports Table Number(s)
16.2.1	All Participants	Final Study Disposition	14.1.1.1 14.1.1.2
16.2.2	All Participants	Inclusion/Exclusion Criteria	N/A
16.2.3	All Participants	Demographic Characteristics	14.1.2
16.2.4	All Participants	Medical History	14.1.3
16.2.5	All Participants	Physical Examination Findings	N/A
16.2.6.1	All Participants	Protocol Deviations	14.1.5.1-2
16.2.6.2	All Sites	Site-Specific Protocol Deviations	14.1.5.3
16.2.7	All Participants	Prior and Concomitant Medications	14.1.4 14.3.5
16.2.8	Safety	Study Medication Dose Administration	N/A
16.2.9.1	All Participants	Adverse Events	14.3.1
16.2.9.2	All Participants	Serious Adverse Events	14.3.1
16.2.9.3	All Participants	Adverse Events Leading to Death	N/A
16.2.10.1	All Participants	Outcomes of Special Interest	14.3.2
16.2.10.2	All Participants	Other Events of Special Interest	14.2.3

Listing Number	Population	Listing Title / Summary	Supports Table Number(s)
16.2.11	All Participants	Clinical Laboratory Results	14.3.3
16.2.12	All Participants	Microbiology Cultures	14.3.4
16.2.13	All Participants	Urine I-FABP/Creatinine Biomarker Data	14.3.6
16.2.14	All Participants	Clinical Cure Score and Overall Therapeutic Success	14.2.1, 14.2.2

13 APPENDIX A – PHARMACOKINETIC ANALYSIS PLAN

1. Purpose

To describe the PK analysis methodology.

2. Pharmacokinetic Analysis Methodology

A PK dataset will be created by the Data Coordinating Center (DCC) to include plasma drug concentrations, CSF drug concentrations, dosing information, and clinical data for each subject enrolled in the trial. The PK profiles for each study drug will be constructed from the observed drug concentration-time data.

For each study drug, a population PK analysis will be performed using the PK dataset to determine compartmental population PK parameters (i.e. clearance and volume) with the program NONMEM (Icon Corp., MD). A base structural PK model (i.e. 1 compartment) will be developed to describe the PK data. Additional structural models (i.e. 2 compartments) will be explored if justified by the data and existing literature. A covariate analysis will be performed to determine the influence of clinical factors (GA, PNA, PMA, weight, serum creatinine, albumin, hematocrit, and concomitant medications) on PK parameter estimates. For metronidazole and clindamycin, the covariate analysis will also include evaluation of the effect of genetic polymorphisms in CYP450 enzymes, if available, on PK parameter estimates. A forward addition, backward elimination method will be used to incorporate significant covariates into the model. In addition, inter-subject and residual variability will be quantified. Post-hoc Bayesian individual PK parameters will then be estimated for each subject. The final population PK model will be evaluated via bootstrapping and visual predictive check techniques. The final population PK parameters and their associated variability will be incorporated as the input model to assess achievement of the predefined surrogate efficacy target and to assess optimal study drug dosing in infants using Monte Carlo simulations.

For infants in group 5 with CSF concentration data, the population PK analysis will be used to predict plasma concentrations at the time of CSF concentrations. The CSF to plasma concentration ratio will be calculated with these 2 values. If data permits, determination of CSF PK parameters (i.e. inter-compartment transfer rates and volume) for metronidazole, clindamycin, and piperacillin-tazobactam will be performed. The base structural models explored for this group may include a CSF compartment in addition to the central compartment.

3. Primary PK Endpoints

- Population PK analysis (Groups 1 – 4)
  - Population clearance (CL)
  - Population volume of distribution (V)
  - Inter-subject variability

- Residual error
- Individual Bayesian post-hoc parameters
  - CL
  - V
  - Half-life

- Population PK analysis (Group 5)
  - CSF:plasma concentration ratios

4. Analysis Population

The analysis population for the population PK analysis will include all subjects with evaluable data that received at least 1 dose of study drug and who had at least 1 PK sample collected.

5. Missing Data

Missing clinical data may be input with the closest value carried forward or back filled for up to 7 days.

6. Figures and Tables

6.1 Tables and Figures for Inclusion in the Clinical Study Report (CSR)

As applicable, tables from the PK report will be copied into the main CSR.

7.2 Tables for the PK Report (Appendix)

The following tables will be generated as applicable by the pharmacology team for the PK report:

- Summary statistics (mean, SD, median, minimum and maximum) of clinical characteristics and continuous covariates by group and overall
- Base and final population PK model structures
- Summary statistics of post-hoc individual PK parameters overall and by age group/special population
- Summary statistics of simulation results
- Model development table including model file, estimation method, fixed effects, random effects, point estimates
- Base and final population PK model parameters including bootstrapped 95% CI

7.3 Figures for the PK Report

The following figures will be generated as applicable by the pharmacology team for the PK report:

- Population PK model goodness of fit plots for the base and final models
- Visual predictive checks
- Box plots of relevant covariates vs. study groups
- Scatter plots of relevant continuous covariates vs. study groups
- Histograms of time after dose and drug concentrations
- Scatter plot of drug concentration vs. time after dose overall and by group
- Individual time vs. concentration profile including observed and predicted concentrations
- Scatter plots of relevant covariates vs. empirical Bayesian estimates
- Scatter plots of PK parameters vs. covariates
- Box plots of PK parameters by study group

7.4 Listings for the PK Report (Appendix)

The following listings will be generated as applicable by the pharmacology team for the PK report:

- Clinical characteristics and covariates for subjects
- Drug concentrations, predicted concentrations, and residuals for all subjects
- Post-hoc individual PK parameters for all subjects
- Bootstrap parameter and variance results for all subjects
- Excluded samples