Pediatric Trials Network

Ampicillin Pharmacokinetics and Safety in Infants

NICHD-2012-AMP01

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Principal Investigator (IND Sponsor):	Daniel K. Benjamin Jr., MD, PhD, MPH Professor of Pediatrics Duke University Medical Center 2400 Pratt St., Durham, NC 27705 Redacted

Statement of Compliance

This trial will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (human subjects protection), 21 CFR 312 (Investigational New Drug), 21 CFR part 50 (informed consent), and 21 CFR part 56 (institutional review board [IRB]).

All individuals responsible for the design and/or conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the investigator brochure or product label, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all subjects with informed consent forms, as required by government and International Conference on Harmonization regulations. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, part 312.64.

Principal Investigator (Print Name)

Signature Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

The signature below documents the review and approval of this protocol and the attachments (e.g., package inserts), and provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

Pediatric Trials Network
Study Principal Investigator (Print Name)

Signature

Date

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BP	Blood Pressure
BPCA	Best Pharmaceuticals for Children Act
BUN	Blood Urea Nitrogen
BMP	Basic Metabolic Panel
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMP	Comprehensive Metabolic Profile
C_{max}	Maximum Concentration
C_{0h}	Observed Concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSF	Cerebrospinal fluid
DBS	Dried Blood Spot
DCC	Data Coordinating Center
DCF	Data Collection Form
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GA	Gestational Age
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee

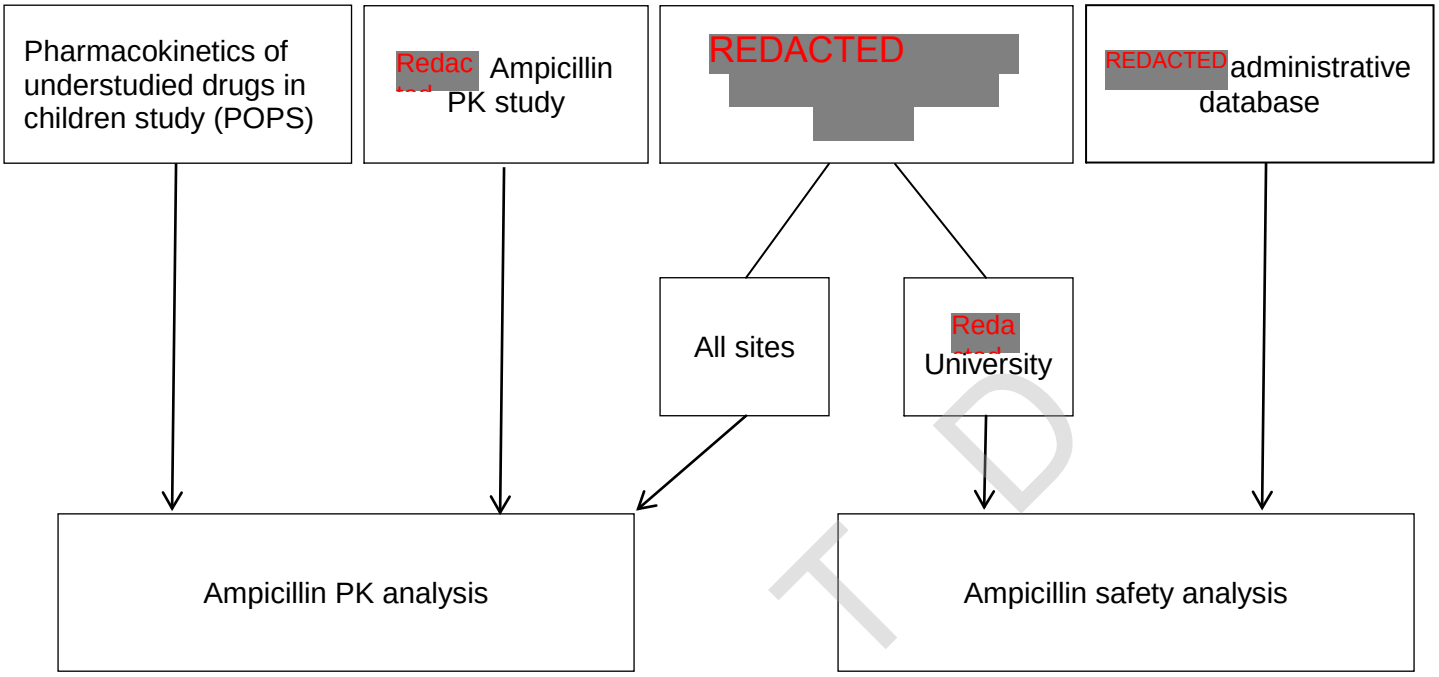
List of Abbreviations - *continued*

IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IVH	Intraventricular Hemorrhage
JAMA	Journal of the American Medical Association
kg	Kilogram
MedDRA ®	Medical Dictionary for Regulatory Activities
mg	Milligram
µg	Microgram
MOP	Manual of Procedures
N	Number (typically refers to participants)
NDA	New Drug Application
NEC	Necrotizing Enterocolitis
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs
PD	Pharmacodynamics
PDA	Patent Ductus Arteriosus
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PTN	Pediatric Trials Network
PPRU	Pediatric Pharmacology Research Unit
QA	Quality Assurance
QC	Quality Control
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
SM	Safety Monitor
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WBC	White Blood Count
WHO	World Health Organization

Protocol Synopsis

Protocol Title:	**Ampicillin Pharmacokinetics and Safety in Infants**
Phase:	N/A
Product:	Ampicillin
Objectives:	1. Characterize the PK of ampicillin from samples obtained in previously conducted or ongoing PK studies of ampicillin 2. Characterize safety of ampicillin prescribed to infants per standard of care by their treating caregiver
Study Design:	Secondary data analysis of PK , retrospective safety chart review and administrative database review for safety evaluation
Study Population:	Infants admitted to the intensive care nursery and received ampicillin administered per standard of care by their treating caregiver. No participants will be enrolled in this protocol
Number of Participants:	Dataset will include approximately 200 for PK analysis Dataset will include approximately 400,000 for safety analysis
Number of Sites:	No new participants will be enrolled in this protocol
Duration of Participant Participation:	No new participants are being enrolled in this protocol.
Dose Schedule:	Infants receiving ampicillin per standard of care as administered by their treating caregiver; the prescribing of drugs to infants will not be part of this protocol.
Estimated Start:	March 2012
Estimated Time to Complete Enrollment:	No new participants will be enrolled in this protocol.

Schematic/Description of Study Design



1 KEY ROLES

For questions regarding this protocol, contact:

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Ampicillin Therapy for Bacterial Sepsis in Infants

Bacterial sepsis remains a leading cause of death in infants admitted to neonatal intensive care units (NICUs). The incidence of early onset sepsis (<4 postnatal days) in infants admitted to the NICU is 1.2% to 2% and for late onset sepsis (4-120 postnatal days) 14% to 36%. The incidence of late onset sepsis is higher in very low birth weight infants (VLBW, birth weight <1500 g) [1,2]. The most commonly administered medication in the NICU, with an exposure rate of 693 per 1000 NICU-discharged infants, is ampicillin [3]. Ampicillin is a beta-lactam antibiotic approved by the FDA to treat local and disseminated infections caused by susceptible organisms in patients of all age groups [4].

2.1.2 Ampicillin PK and Safety in Infants

The PK of ampicillin has been studied in children and adults [5-18], but data on dosing in the neonatal population are sparse. The first pharmacological studies of serum and cerebrospinal fluid concentrations after intramuscular injection of ampicillin in term and preterm (<2500 g) infants, were performed between 1967 and 1974. These studies included a combined total of 156 infants (gestational age not specified) and showed that the serum half-life of ampicillin decreases rapidly in the first two weeks of life as a result of increasing clearance. Doses studied ranged from 25-150 mg/kg, administered every 8-12 hours according to postnatal age [12-14]. A later study assessed the PK of ampicillin in 142 preterm infants with a gestational age (GA) $\geq$ 24 weeks. The study concluded that infants with a GA $\leq$ 28 weeks required a dosing interval of 18-24 hours and did not require initial dosing exceeding 50 mg/kg [15]. Current dosing regimens take into account the gestation and postmenstrual age related variation in renal drug clearance, and recommend lower doses and less frequent dosing in the most premature infants [11]. However, the available data in the literature is insufficient to support dosing of ampicillin in the most extreme premature infants (≤32 weeks gestational age at birth).

Although ampicillin is the most commonly administered medication in the NICU, its safety in the neonatal population is poorly described. Adverse events (AE) listed on the FDA label for ampicillin are not specific to the neonatal population. Ampicillin AEs are mostly due to sensitivity phenomena that are more common in people with a history of penicillin exposure. This is very uncommon in the neonatal population. In a recent study comparing clinical efficacy of ampicillin or penicillin in combination with gentamicin therapy for early onset sepsis in infants (including GA <26 weeks), both were well tolerated with no difference in AEs or laboratory abnormalities. However, the focus of this study was clinical effectiveness comparison, and not safety profiling [15]. Among the potential serious AEs in infants is the risk of ampicillin induced seizures [4]. As with other penicillin's, β-Lactam-induced neurotoxicity is of concern if cerebrospinal fluid concentrations of ampicillin are high. This has been reported in adult case reports, but the incidence of seizures in infants, treated with ampicillin, has not been evaluated [16, 17]. Another

known side-effect of ampicillin most commonly seen after repeated dosing is inhibition of the coagulation cascade. The prevalence of this AE in the neonatal population, which is at risk of coagulopathy, is unknown [18]. Overall, given the importance of safety and improved long term outcomes in the neonatal population, a more detailed description of the safety of this commonly used antibiotic is warranted.

2.1.3 Recent Ampicillin PK and Safety Trials in Infants

2.1.3.1 Pediatric Pharmacology Research Unit (PPRU) Study

In order to fill knowledge gaps in neonatal drug dosing, the NIH-sponsored pediatric pharmacology research unit (PPRU) conducted the Antimicrobial Pharmacokinetics (PK) in Premature Infants Trial [Jan. 2006 to Nov. 2010]. This multi-center, open-label, opportunistic study collected PK samples from premature infants <32 weeks gestational age who were receiving ampicillin per standard of care.

2.1.3.2 Pharmacokinetics of Understudied Drugs in Children Study (POPS)

This prospective multi-center trial is conducted within the Pediatric Trials Network (PTN) to characterize the PK of understudied drugs administered to children per standard of care by their treating caregiver. The study will enroll a total of 500 participants at approximately 15 sites; a subset of those will receive ampicillin.

2.1.3.3 Redacted Ampicillin PK Study

In order to better understand the pharmacokinetics of ampicillin and the relationship between ampicillin and the organic anion transporters, 60 infants (≥ 24 weeks gestational age and up to 120 days postnatal age) receiving ampicillin per standard of care were enrolled in an open-label, opportunistic study.

2.2 Scientific Rationale

Despite the common use of ampicillin in infants admitted to the NICU, PK and safety studies to define optimal dosing are lacking. Challenges associated with clinical trials in infants limit the ability to conduct large PK and dosing trials in this population. Capitalizing on all available data sources to characterize the PK and safety of ampicillin used in infants is therefore essential. The purpose of this study is to characterize the PK and safety of ampicillin administered to infants per standard of care as administered by their treating caregiver. This study will analyze PK samples previously obtained in the PPRU Antimicrobial PK in Premature Infants Trial, POPS and Redacted ampicillin PK studies. In addition, safety data will be obtained from the subset of patients enrolled in the PPRU study at Redacted, and from the Pediatrix Medical Group Database. The data evaluated through this initiative will provide valuable PK and safety information for the use of ampicillin in infants. The project will not involve prescribing study drug or biological sample collection from infants. This principle will allow for a minimal risk study and maximize interpretation of available data.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The administration of study drug or the collection of study sample from infants is not a part of this study. The only risk is potential breach of confidentiality. However, data obtained from the Pediatrix administrative database is completely deidentified prior to receipt by DRCI. Data from the PPRU and POPS studies will be coded; participants will be identified by code numbers and not by name. Data obtained from the Redac study will be de-identified. Access to data received at DCRI will be limited to study team members only. The computer network is protected by a firewall. Data from chart review will be captured via secured eCRF at the BPCA DCC (EMMES). Passwords to eCRF are assigned centrally and associated with specific permissions to control access, which will be closely tracked and monitored. To protect against the risk of loss of confidentiality, the study follows the procedures specified by Duke University Hospital System IRB for maintaining confidentiality.

2.3.2 Potential Benefits

Conclusions drawn from this study will benefit infants receiving treatment with ampicillin in the future through optimization of dosing regimen and better characterization of ampicillin safety profile.

3 OBJECTIVES

3.1 Study Outcome Measures

The purpose of this study is to evaluate the PK and safety profile of ampicillin administered to infants per standard of care by their treating caregiver. The PK of ampicillin will be evaluated through the analysis and evaluation of PK data obtained from 3 PK studies of ampicillin in infants (PPRU, POPS, Redac ted ampicillin study). The safety profile of ampicillin will be evaluated through analysis and interpretation of safety data available from a subset of infants enrolled in one of the PK studies (PPRU Antimicrobial Pharmacokinetics (PK) in Premature Infants Trial at Reda cted) and from data collected on all infants administered ampicillin per standard of care by their caregiver while admitted in one of the 323 NICUs managed by the Pediatrix Medical Group.

4 STUDY DESIGN

1) Objective #1

Prospective PK study using samples collected during the PPRU Antimicrobial Pharmacokinetics (PK) in Premature Infants Trial, POPS and Redac ampicillin PK study. The samples from the PPRU and Redac trials have been collected, labeled and tested as previously described in the individual study protocols. Analysis of these samples will be conducted by the Redac pharmacology laboratory. Samples from the POPS study are currently being collected and will be sent to the study core laboratory for analysis.

2) Objective #2

A review of all infants enrolled in the PPRU Antimicrobial Pharmacokinetics (PK) in Premature Infants Trial at Redacted will be conducted to identify the presence of safety events of interest in infants receiving ampicillin while enrolled in the PPRU study. In addition, a review of all infants in the Pediatrix Medical Group administrative database will be conducted to identify safety events occurring while on ampicillin versus when not on ampicillin.

5 Study Population

5.1 Selection of the Study Population

5.1.1 Objective #1

No new participants will be enrolled in this study. Instead, samples from all infants who received ampicillin while enrolled in the PPRU Antimicrobial Pharmacokinetics (PK) in Premature Infants Trial, POPS and Redac ted ampicillin PK study will be analyzed and evaluated. This dataset will include approximately 200 infants stratified by GA and PNA (Table 1). Each group in Table 1 will include at least 16 participants; however, the PK analysis may include infants outside of these groups.

Table 1: Study Population for Objective#1 by Gestational Age (GA) and Postnatal Age (PNA)

GA	PNA
≤ 34 weeks	≤7 days
	8-28 days
> 34 weeks	≤7 days
	8-28 days

5.1.2 Objective #2

All infants who received ampicillin while enrolled in the PPRU Antimicrobial Pharmacokinetics (PK) in Premature Infants Trial at Redacted and infants treated in a NICU managed by the Pediatrix Medical Group between 1997 and 2010 who did or did not receive ampicillin per standard of care. This will include approximately 60 infants from the PPRU study and approximately 400,000 infants from the Pediatrix database.

5.2 Inclusion/Exclusion Criteria

Inclusion criteria:

Objective #1:

- All infants with evaluable PK samples and receiving ampicillin while enrolled in the PPRU Antimicrobial PK in High Risk Infants study, the POPS study, and the Redac ted ampicillin PK study.

Objective #2:
- Infants enrolled in the PPRU Antimicrobial PK in High Risk Infants study at Redacted and infants discharged from a NICU managed by the Pediatrix Medical Group between 1997 and 2010.

Exclusion criteria include:

Objective #1:
- None.

Objective #2:
- None

5.3 Treatment Assignment Procedures (if applicable)

Not applicable.

5.3.1 Replacement Participants

Not applicable.

5.3.2 Randomization Procedures

Not applicable.

5.3.3 Masking Procedures

Not applicable.

5.3.4 Reasons for Participant Withdrawal

Not applicable

5.3.5 Participant Withdrawal from Investigational Product

Not applicable

5.3.6 Handling of Withdrawals

Not applicable

5.3.7 Termination of Study

This study may be terminated at any time by the PI in consultation with NICHD.

6 STUDY PROCEDURES

6.1 Summary of Procedures

6.1.1 Objective #1

A PK database will be created with information from PK samples collected and analyzed through the PPRU Antimicrobial PK in High Risk Infants study, the POPS study, and the Redacted ampicillin PK study. Ampicillin concentrations will be measured with a validated bioanalytical assay. The following demographic and clinical variables will be added to the PK database as applicable (if available) for each data source:

- Date of birth
- Gestational age at birth
- Weight at birth
- Length at birth
- Head circumference at birth
- Apgar score
- Postnatal age
- Ethnicity
- Race
- Gender
- Date and time of ampicillin administration
- Dose amount
- Dosing weight
- Current weight
- Date and time of PK sampling
- Sample type (i.e. scavenged vs. timed)
- Sampling tube type (i.e. EDTA vs. sodium heparin)
- Serum creatinine
- Concomitant medications of interest

6.1.2 Objective #2

6.1.2.1 REDACTED PPRU Antimicrobial PK Study

Data will be extracted from the medical record of participants enrolled at Redacted in the PPRU Antimicrobial PK in High Risk Infants study. The following clinical and demographic variables will be included in addition to date of birth, gestation age, race, ethnicity, sex, and birth weight (Table 2).

Table 2: Variables Collected for Reda cted Safety Study

	Date of birth	-3 days	-2 days	-1 day	On ampicillin	+1 day	+2 days	+3 days
Demographics								
Weight	X			X		X		
Length	X			X		X		
Head circumference	X			X		X		
Adverse Events (new onset)								
Cardiorespiratory arrest					X			
Hypotension					X			
Tachypnea					X			
Tachycardia					X			
Medical NEC					X			
Surgical NEC					X			
Focal intestinal perforation					X			
Grade II IVH					X			
Grade III or IV IVH					X			
Periventricular leukomalacia					X			
Cystic periventricular leukomalacia					X			
PDA requiring medical treatment					X			
PDA requiring surgical treatment					X			
Rash					X			
Seizure					X			
ROP requiring laser surgery					X			
Hyperbilirubinemia requiring exchange transfusion					X			
Laboratory Values*								
AST		X	X	X	X	X	X	X
ALT		X	X	X	X	X	X	X
WBC count		X	X	X	X	X	X	X
Hematocrit		X	X	X	X	X	X	X
Platelets		X	X	X	X	X	X	X
BUN		X	X	X	X	X	X	X
Creatinine		X	X	X	X	X	X	X
Physical Exam								
Abnormality				X	X			
Positive Blood/Urine/CSF Cultures								
Organism		X	X	X	X	X	X	X
Antimicrobial sensitivities		X	X	X	X	X	X	X
Ampicillin dosing**								
Date/time					X			
Dose (mg)					X			

* If laboratory value obtained on start day of ampicillin course, time of day should be recorded.

** Only start of/changes in/last dose of ampicillin dosing/frequency associated with the ampicillin course in which PK samples were obtained will be recorded.

6.1.2.2 Pediatrix Administrative Database Review

Data will be extracted from the Pediatrix Medical Group Database. The following clinical and demographic variables will be included in addition to date of birth, gestation age, race, ethnicity, sex, and birth weight (Table 3).

Table 3: Variables Collected for Pediatrix Safety Study

	Date of birth	-3 days	-2 days	-1 day	On ampicillin	+1 day	+2 days	+3 days
Adverse Events (new onset)								
Cardiorespiratory arrest					X			
Hypotension					X			
Tachypnea					X			
Tachycardia					X			
Medical NEC					X			
Surgical NEC					X			
Focal intestinal perforation					X			
Grade II IVH					X			
Grade III or IV IVH					X			
Periventricular leukomalacia					X			
Cystic periventricular leukomalacia					X			
PDA requiring medical treatment					X			
PDA requiring surgical treatment					X			
Rash					X			
Seizure					X			
ROP requiring laser surgery					X			
Hyperbilirubinemia requiring exchange transfusion					X			
Laboratory Values								
AST		X	X	X	X	X	X	X
ALT		X	X	X	X	X	X	X
GGT		X	X	X	X	X	X	X
Direct bilirubin		X	X	X	X	X	X	X
WBC count		X	X	X	X	X	X	X
Neutrophil count		X	X	X	X	X	X	X
Hematocrit		X	X	X	X	X	X	X
Platelets		X	X	X	X	X	X	X
BUN		X	X	X	X	X	X	X
Creatinine		X	X	X	X	X	X	X
Glucose		X	X	X	X	X	X	X
Sodium		X	X	X	X	X	X	X
Potassium		X	X	X	X	X	X	X
Calcium		X	X	X	X	X	X	X
Magnesium		X	X	X	X	X	X	X
Phosphorus		X	X	X	X	X	X	X
Base excess		X	X	X	X	X	X	X
Positive Blood/Urine/CSF Cultures								
Organism		X	X	X	X	X	X	X
Ampicillin Dosing								
Days of administration					X			
Clinical Variables								
Mechanical ventilation					X			
Fraction of inspired oxygen					X			
Concomitant medications					X			

6.2 Enrollment/Baseline

No new participants will be enrolled in this protocol.

6.3 Follow-up

No participants will be enrolled in this protocol and there will be no follow-up visits.

6.4 Final Study Visit

No participants will be enrolled in this protocol and there will be no study related visits.

6.5 Follow-up Safety Phone Call

No participants will be enrolled in this protocol, and there will be no follow-up safety phone calls.

6.6 Early Termination Visit

No participants will be enrolled in this protocol and there will be no study related visits.

6.7 Unscheduled Visit

No participants will be enrolled in this protocol and there will be no study related visits.

6.8 Laboratory Evaluations

There will be no new laboratory evaluations performed.

7 STUDY PRODUCT DESCRIPTION

Drug of interest in this protocol is ampicillin.

7.1 Dosage and Study Drug Information

The administration of ampicillin study drug is not a part of this protocol.

7.2 Preparation and Administration of Study Intervention/Investigational Product

The administration of a study intervention/investigational product is not a part of this protocol.

7.3 Modification of Study Intervention/Investigational Product for a Participant

The administration of a study intervention/investigational product including any modification is not a part of this protocol.

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

The administration of a study intervention/investigational product is not a part of this protocol.

7.5 Assessment of Participant Compliance with Study Intervention/Investigational Product

No participants will be enrolled in this protocol and the administration of study intervention/investigational product is not a part of this protocol.

7.6 Concomitant Medications/Treatments

No concomitant medications or treatments will be administered in this protocol.

8 ASSESSMENT OF SAFETY

No participants will be enrolled in this protocol. The administration of ampicillin or concomitant medications, and collection of samples is not part of this protocol. Thus, there will be no separate assessment of safety other than what is described under the primary outcome measures.

8.1 Discontinuation Due to Adverse Events

No participants will be enrolled in this protocol, thus no discontinuation due to adverse events will occur.

8.2 Reporting Procedures

No participants will be enrolled in this protocol, and no new reportable safety data will be collected. Thus, no AEs reporting procedure is included in this protocol.

8.3 Type and Duration of Follow-up of Participants after Adverse Events

No participants will be enrolled in this protocol. Thus, no follow-up of participants after AEs will be conducted once infants are discharged from the hospital.

8.4 Halting Rules

No participants will be enrolled in this protocol. Thus, no halting rules are included in this protocol.

8.5 Safety Oversight (SM plus DMC)

No participants will be enrolled in this protocol. Thus, no safety oversight is included in this protocol.

9 CLINICAL MONITORING

No participants will be enrolled in this protocol. Thus, no clinical monitoring is included in this protocol.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size

10.1.1 Objective #1

This objective will include approximately 226 infants from the PPRU Antimicrobial PK in High Risk Infants study, approximately 34 infants from the POPS study and approximately 53 infants from the Redacted ampicillin PK study

10.1.2 Objective #2

We anticipate data from approximately 400,000 infants who received ampicillin and 300,000 infants who did not receive ampicillin in the Pediatrix Medical Group Database. In addition, retrospective chart review will be performed on an additional 60 infants who received ampicillin while enrolled in the PPRU study at Redacted.

10.2 Planned Interim Analyses (if applicable)

There will be no planned interim analysis in this protocol.

10.3 Participant Enrollment and Follow-Up

No new participants will be enrolled in this protocol and there will be no follow up.

10.4 Analysis Plan

10.4.1 Objective #1

A combined PK dataset will be created to include drug concentrations and dosing information for each participant with evaluable ampicillin PK samples enrolled in the PPRU Antimicrobial PK in High Risk Infants study, the POPS study, and the Redacted ampicillin PK study. A population PK analysis will be performed on the PK data to determine compartmental population PK parameters (i.e. clearance and volume of distribution) with the program NONMEM version VII (Icon Corp., MD). A base structural PK model (i.e. one compartment) will be developed to describe the PK data. Additional structural models (i.e. 2 compartments) will be explored if justified by the data. A covariate analysis will be performed to determine the influence of clinical factors (e.g., GA, PNA, weight, serum creatinine) on PK parameter estimates. In addition, inter-participant and residual variability will be quantified. Post-hoc Bayesian individual PK parameters will then be estimated for each participant. The final population PK parameters and their associated variability will be evaluated via visual predictive check and bootstrapping. In addition, ampicillin dosing strategies will be explored using Monte Carlo simulations.

10.4.2 Objective #2

Severity of diagnoses and laboratory values will be assigned according to predetermined definitions (see Appendix tables 4 and 5). A diagnosis (Appendix table 4) will be attributed to ampicillin if it was first made on a day that the infant was exposed to ampicillin. A laboratory abnormality (Appendix table 5) will be attributed to ampicillin if it occurred on a day that the infant was exposed to ampicillin or one day after exposure to ampicillin. For the cohort of patients from the PPRU Antimicrobial PK in High Risk Infants study enrolled at Reda cted, the frequency of diagnoses and laboratory abnormalities attributed to ampicillin will be described using standard summary statistics. For the patients exposed to ampicillin in the Pediatrix database, the frequency of diagnoses and laboratory abnormalities attributed to ampicillin will be compared to those not attributed to ampicillin. Multivariable logistic regression analyses will be performed to evaluate the association between diagnoses and laboratory abnormalities and ampicillin controlling for clinical factors associated with poor outcome in infants such as mechanical ventilation, inotropic support, and demographic features including race, gender, gestational and postnatal age. Outlier diagnostics and evaluation for multicollinearity will be performed using standard techniques. The full model containing all clinically relevant variables listed above will be compared to scaled down models using likelihood ratio tests, and the most parsimonious model that fits the data will be used for analysis. The odds of a diagnosis or laboratory abnormality occurring on a day the infant was exposed to ampicillin will be compared to the odds of occurrence on a day the infant was not exposed to ampicillin. Odds ratios and 95% confidence intervals derived from this model will be reported.

11 PARTICIPANT CONFIDENTIALITY

No participants will be enrolled into this protocol. No samples will be collected as a part of this study. Human participant data obtained during retrospective chart review will not be identifiable directly or through secondary identifying information. Participant confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor(s) and their agents. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any third party without prior written approval of the sponsor. Participant information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated by HIPAA (Health Insurance Portability and Accountability Act) and as mandated in Title 45 CFR Parts 160 and 164. All data records will be kept confidential, and the participant's name will not be released at any time. Participant data records will not be released to anyone other than the Sponsor or its designees and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the participant's privacy is guaranteed.

12 INFORMED CONSENT PROCESS

This study does not involve the enrollment of participants, thus no informed consent is required. The Safety evaluation via a review of medical charts by the PI or their representatives cannot be practically performed if informed consent is required of each participant. Therefore, a waiver of informed consent for the retrospective chart review will be requested from the Institutional Review Board (IRB).

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

During the chart review process, each participating site will meet regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Data collection forms will be derived from the eCRFs and provided by EMMES, the Data Coordinating Center (DCC), to assist chart review.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site. The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

15.1 Ethical Standard

The investigator will ensure that the study will be conducted in accordance with the protocol, the ethical principles of Good Clinical Practice (ICH E6) that have their origin in the Declaration of Helsinki, and all applicable local regulations. The investigator will ensure the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs.

15.2 Institutional Review Board

The investigator will ensure that the protocol is reviewed and approved by the appropriate Institutional Review Board (IRB) prior to the start of any study activities. The IRB will be appropriately constituted and will perform its functions in accordance with FDA regulations, ICH GCP guidelines, and local requirements as applicable.

15.3 Participant Confidentiality

No participants will be enrolled in this protocol. Data obtained from the PPRU, POPS, and Redac studies will be used for the analyses detailed in this protocol. Data obtained from the PPRU, Redact and POPS studies will be coded; participants will be identified by code numbers and not by name. Data obtained from the Pediatrix database will be de-identified as defined by the HIPAA Privacy Rule (45 CFR 164.514 (a) and (b)).

Appropriate and adequate provisions for ensuring participant privacy and data confidentiality will be maintained by the participating investigators, their staff, the sponsor(s), and their agents. The study protocol, documentation, data, and all other information generated by this study will be maintained in a secure manner and will be kept confidential as required by law. Data access will be limited to study personnel and the data will be stored on servers which have limited physical access (e.g. locked rooms) and limited electronic access (e.g. password controlled access to data, computers and, if applicable, networks). No information concerning the study or the data will be released to any third party without prior written approval of the sponsor.

Study records, including medical and pharmacy records, may be reviewed in order to meet federal or state regulations. Reviewers may include the Food and Drug Administration (FDA), IRBs, the sponsor and its representatives, or the NIH.

15.4 Study Discontinuation

Not applicable. No participants will be enrolled in this study. Prescription of study drug is not part of this protocol.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization, Good Clinical Practice, Consolidation Guideline.

During chart review, the investigator(s) at participating site(s) will ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF should be consistent with the data collection form/source documents, or the discrepancies should be documented. DCRI and/or EMMES will provide guidance to investigators on making corrections to the data collection forms and eCRFs.

16.1 Data Management Responsibilities

All data collection forms must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

The EMMES Corporation will serve as the DCC for this study and will be responsible for data management, quality review, analysis, and reporting of the study data

16.2 Data Capture Methods

Clinical data (including AEs) obtained through chart review will be entered into a 21 CFR Part 11-compliant internet data entry system provided by the EMMES Corporation. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the data collection forms/source documents.

16.3 Types of Data

Data for this study will include PK and safety.

16.4 Timing/Reports

Not applicable

16.5 Study Records Retention

Records and documents pertaining to the conduct of this study will be stored for a minimum of 2 years following the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

16.6 Protocol Deviations

Not applicable

16.7 Participant Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants of clinical trials.

17 PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal under the oversight of the Publication Committee of the Pediatric Trials Network. The PTN Publication Committee comprises representatives of the network cores, thought-leaders, DCC, and PTN and is responsible for generation and coordination of the publications that report scientific findings of the network. All public presentations (abstracts, manuscripts, slides and text of oral or other presentations, and text of any transmission through any electronic media) by participating investigators, participating institutions, DCC, and PTN that use PTN data and are intended to represent the PTN or are supported by the PTN will be reviewed by the Publication Committee per the Publication Committee charter.

The Publication Committee guarantees that the study results are presented by experts in the field that have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The committee goals are to ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included.

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journal. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before patient enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:
http://publicaccess.nih.gov/
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html

18 LITERATURE REFERENCES

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19 APPENDIX

Table 4. Diagnoses

Body System	Diagnoses	Serious Diagnoses
Gastrointestinal	Medical NEC	Surgical NEC
		Focal intestinal perforation
Neurologic	Grade II IVH	Grade III or IV IVH
	Periventricular leukomalacia	Cystic periventricular leukomalacia
		Seizure
Cardiovascular	PDA requiring medical treatment	PDA requiring surgical treatment
	Hypotension requiring pressors	Cardiorespiratory arrest
	Tachycardia	
Ophthalmology		ROP requiring laser surgery
Hematology		Hyperbilirubinemia requiring exchange transfusion
Dermatology	Rash	
Respiratory	Tachypnea	

IVH=intraventricular hemorrhage NEC=necrotizing enterocolitis
PDA=patent ductus arteriosus ROP=retinopathy of prematurity

Table 5. Laboratory Values

Laboratory Values	Abnormality	Serious Abnormality
Serum Electrolytes		
Hypoglycemia	< 40 mg/dL	< 20 mg/dL
Hyperglycemia	> 250 mg/dL	> 400 mg/dL
Hyponatremia	< 125 mmol/L	< 115 mmol/L
Hypernatremia	> 150 mmol/L	> 160 mmol/L
Hyperkalemia	> 6 mmol/L	> 7.5 mmol/L
Hypokalemia	< 3 mmol/L	< 2.5 mmol/L
Hypercalcemia (iCa)	> 12.5 mg/dL (>1.5 mmol/L)	> 13.5 mg/dL (>1.6 mmol/L)
Hypocalcemia (iCa)	< 6.0 mg/dL (<0.9 mmol/L)	< 5.0 mg/dL (< 0.8 mmol/L)
Hypermagnesemia	> 3.5 mg/dL	> 4.5 mg/dL
Hypomagnesemia	< 1.5 mg/dL	< 1.2 mg/dL
Hyperphosphatemia	> 9.5 mg/dL	> 10.5 mg/dL
Hypophosphatemia	< 3.5 mg/dL	< 2.5 mg/dL
Base Excess	< -10 mmol/L	< -15 mmol/L
Renal Dysfunction		
Elevated BUN	> 70 mg/dL	> 100 mg/dL
Elevated Creatinine	> 1.7 mg/dL	> 3.0 mg/dL
Liver Dysfunction		
Elevated AST	> 5 x upper limit of normal	> 10 x upper limit of normal
Elevated ALT	> 5 x upper limit of normal	> 10 x upper limit of normal
Elevated GGT	> 5 x upper limit of normal	> 10 x upper limit of normal
Direct bilirubin	> 5 mg/dL	>10 mg/dL
Complete Blood Count		
Leukocytosis	> 25,000/mm3	> 40,000/mm3
Leukopenia	< 5000/mm3	< 2000/mm3
Neutropenia	< 500/mm3	< 100/mm3
Thrombocytopenia	< 100/mm3	< 30/mm3
Thrombocytosis	> 600,000/mm3	> 1,000,000/mm3