Title:	**Multiple Dose Pharmacokinetic Study of Meropenem in Young Infants (<91 days) with Suspected or Complicated Intra-abdominal Infections**
Protocol Number:	**NICHD-2005-18**
Study Drug:	**Meropenem**
IND Number:	**101,043**
Phase:	**II**
Sponsor:	**NICHD**
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Final Date:	**28 March 2008**

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PROTOCOL SYNOPSIS

Protocol Title	Multiple Dose Pharmacokinetic Study of Meropenem in Young Infants (<91 days) with Suspected or Complicated Intra-abdominal Infections
Sponsor:	NICHD
Product	Meropenem
Objectives:	a. To characterize meropenem single-dose and multiple-dose PK in subjects with suspected or complicated intra-abdominal infections. b. To characterize the safety profile of meropenem in the treatment of suspected or complicated intra-abdominal infections. c. To assess collected efficacy data for meropenem for the treatment of suspected or complicated intra-abdominal infections.
Study Design:	Multi-center, prospective, pharmacokinetic and safety study of meropenem for the treatment of suspected or complicated intra-abdominal infections
Study Population:	Premature and term young infants (<91 days) who have a suspected or early complicated intra-abdominal infection. These subjects must be subdivided into the following four groups: Group 1: GA at birth below 32 weeks - PNA < 2 weeks; Group 2: GA at birth below 32 weeks - PNA ≥ 2 weeks and < 91 days; Group 3: GA at birth 32 weeks or older - PNA < 2 weeks; Group 4: GA at birth 32 weeks or older - PNA ≥ 2 weeks and < 91 days.
Number of Infants:	Approximately 200 infants that complete the study
Number of Sites:	Approximately 25
Treatment:	Meropenem Aminoglycoside should be administered in conjunction with meropenem. Additional antimicrobial coverage may be added per standard of care.
Treatment Duration	At least 3 days; otherwise, per local standard of care (maximum 21 days)
PK/PD:	Minimal sampling and population PK will be employed
Safety:	The protocol will rely on three mechanisms for safety: 1) The DSMB 2) Adverse event and SAE reporting mechanisms 3) The active, daily, real time oversight of the MPODS Clinical Safety Committee All serious adverse events (SAEs) will be closely monitored throughout the course of the study. Seizures will be intensely monitored and clinical laboratories of renal, and hepatic toxicity monitored weekly as available per local standard of care. Safety assessments will include seizure documentation (including correlation of serum meropenem level and seizures), physical examination, clinical laboratory values, LFTs, renal function and nosocomial infections (tracked by pathogen).
Statistical Consideration:	The sample size is designed to assess single and multiple dose PK of meropenem in young infants. All infants who receive meropenem will be analyzed. These infants will comprise the population for the safety analysis, and if any PK samples are obtained, their blood will be evaluated in the PK analysis. Those infants who have an efficacy measurement at Day 28 will also be evaluated for clinical (efficacy) response. Key safety endpoints that will be evaluated in the final analysis: include death, seizures, strictures, perforation, wound dehiscence, short gut, development of extended beta lactamase infection, development of candidiasis, and antimicrobial therapy failure. The proportion of infants affected and 95% CI for each key safety endpoint will be reported. The following PK parameters will be estimated: a) Plasma clearance b) Volume of distribution c) Cmax, Tmax, AUC_{0-T}, (at steady state), Ke and $t_{1/2}$ $AUC_{0-\infty}$ (estimated from the 1st dose)
Inclusion Criteria	a. Written permission from parent or legal guardian b. Age younger than 91 days c. Likely to survive beyond the first 48 hours after enrollment d. Sufficient intravascular access (either peripheral or central) to receive study drug

	AND ONE OF THE FOLLOWING e. 1) Physical, radiological, and/or bacteriological findings of a complicated intra-abdominal infection. These include peritonitis, NEC Grade II or higher by Bell's criteria, Hirschsprung's disease with perforation, spontaneous perforation, meconium ileus with perforation, bowel obstruction with perforation, as evidenced by free peritoneal air on abdominal radiograph, intestinal pneumotosis or portal venous gas on abdominal radiographic examination. OR 2) Possible NEC OR 3) Otherwise receiving meropenem per local standard of care
Exclusion Criteria	a. Renal dysfunction evidenced by urine output <0.5 mL/hr/kg over the prior 24 hours b. Serum creatinine >1.7 mg/dL c. History of clinical seizures or EEG confirmed seizures d. Concomitant treatment with another carbapenem (ertapenem or imipenem) at the time of informed consent e. Any condition which would make the subject or the caregiver, in the opinion of the investigator, unsuitable for the study
ACRONYMS AND ABBREVIATIONSAE	Adverse Event
BPCA-CC	Best Pharmaceuticals for Children Act Coordinating Center
BUN	Blood Urea Nitrogen
C	Drug Concentration
CBC	Complete Blood Count
CONS	Coagulase Negative Staphylococcus
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-reactive Protein
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
DOL	Day of Life
ELBW	Extremely Low Birth Weight
ESBL	Extended Spectrum Beta-Lactamases
FDA	Food and Drug Administration
g/dL	Grams per Deciliter
GA	Gestational Age
GCP	Good Clinical Practice
GNR	Gram Negative Rod
GPC	Gram Positive Cocci
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
IVRS	Interactive Voice Response System
Kg	Kilogram
LFT	Liver Function Tests
Mcg	Microgram
Mg	Milligrams
MIC	Minimum Inhibitory Concentration
mL	Milliliter

MPODS	Meropenem Off-Patent Drug Studies
MRSA	Methicillin Resistant S. aureus
NEC	Necrotizing Enterocolitis
NICHD	National Institute for Child Health and Human Development
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PNA	Postnatal Age
PODS	Pediatric Off-Patent Drug Studies
SAE	Serious Adverse Event
SNAP	Score for Neonatal Acute Physiology
Vd	Volume of distribution
WR	Written Request

1.0 Background and Rationale

1.1 Introduction

Meropenem, a carbapenem, belongs to an antibiotic class that possesses one of the broadest spectra of antimicrobial activity available, including most of the bacterial pathogens responsible for serious, life-threatening infections occurring in young (<91 days) infants. Meropenem is stable against hydrolysis by most extended spectrum beta-lactamases and AmpC chromosomal beta-lactamases underscoring the drug's activity against many antibiotic resistant Gram positive (e.g., penicillin-resistant *S. pneumoniae*) and Gram negative (e.g., *P. aeruginosa*) bacteria. Important indications for meropenem involve infections due to multi-drug resistant pathogens and polymicrobial sepsis. Meropenem is FDA-labeled for pediatric subjects from three months of age through adolescence as single agent antimicrobial therapy for bacterial meningitis and complicated intra-abdominal infections. There is substantial off-label use of meropenem in neonates and infants younger than three months of age. This off-label use occurs despite the lack of adequate meropenem PK, dosing, tolerability and safety data for this vulnerable subject group. The present proposal aims to determine PK and safety of meropenem for the treatment of suspected and complicated intra-abdominal in neonates and infants younger than three months of age.

1.2 Metabolism in Adults

Meropenem mean peak plasma concentrations were approximately 23 µg/mL (range 14-26) for 500 mg single dose and 49 µg/mL (range 39-58) for a 1 g single dose in adult volunteers,. Following intravenous doses of 500 mg in adults mean plasma concentrations of meropenem usually decline to approximately 1 µg/mL at 6 hours after administration. In subjects with normal renal function, the elimination half-life of meropenem is approximately 1 hour. Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/mL are maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function. Plasma protein binding of meropenem is approximately 2%. There is one metabolite which is microbiologically inactive.

1.3 Previous Studies in Children

Two large-scale multi-center randomized studies have been published to date. The first of these compared meropenem to cefotaxime, with or without the addition of metronidazole or amikacin in 170 children 3 months to 12 years. (Schuler 1995) Antibiotics were given empirically for presumed serious bacterial infection. Satisfactory clinical response was achieved in 98% of the meropenem-treated subjects and in 93% receiving one of the cefotaxime regimens. Similar results were obtained in a study of 414 children between 1 month and 12 years given either meropenem or cefotaxime with or with out clindamycin or tobramycin. (Arrieta 1997) Children in the meropenem arm received 10 or 20mg/kg; and illnesses included lower respiratory tract infection, urinary tract infection, septicemia, skin infections, and intra-abdominal infections. Meropenem was similar in efficacy to cefotaxime and ceftriaxone in infants and children with bacterial meningitis. (Odio, 1999)

1.4 Safety

The most commonly reported side effects considered related to meropenem in studies in children have been diarrhea (3.3 to 4.7%), nausea and vomiting (0.4 to 1%), rash (0.8%),

glossitis (tongue swelling) (1%), oral thrush (1.9%) or diaper rash from yeast (3.1%), and redness and swelling at the injection site (0.5%). In comparison trials, these reactions occurred in similar frequency in the comparison (cephalosporin) groups. (Schuler 1995, Bradley 1996) Similar results have also been observed in clinical trials of adult subjects.

The potential for adverse CNS effects, particularly seizures, has been carefully studied with meropenem in older subjects. All beta-lactam antibiotics have the potential to cause neurotoxicity. The mechanism for this adverse effect is believed to be competitive inhibition of gamma-aminobutyric acid (GABA). Imipenem has been linked to the development of seizures for several years. In adults, the incidence of this adverse effect has been as high as 3% in some reports. In children, neurotoxicity with imipenem has also been reported. Meropenem has less affinity for GABA receptors and has been found to cause less neurotoxicity than imipenem both in animal models and during clinical trials. In trials comparing meropenem to cephalosporin regimens, the incidence of seizures was not significantly different between groups. The only seizures reported in meropenem-treated pediatric subjects to date have occurred during treatment for meningitis. No cases have been reported in children treated for non-CNS infections. (Bradley 1996)

1.5 Studies in Young Infants

Van Enk et al. reported the results from 7 preterm infants (gestational ages 27-32 weeks, chronological ages 5-44 days) who were treated for infections with meropenem at a dose of 15 mg/kg every 12 hours (Van Enk, 2001). Meropenem PK parameter estimates were highly variable and significantly different from older infants, age 2-5 months (Blumer 1995, Blumer 1996, Parker 1995). Meropenem clearance in these 7 neonates was 40% less and Vd 50% greater than infants, resulting in an average half-life twice that of older infants.

Two studies have been recently completed studies in young infants. The first study evaluated single dose PK of meropenem (10, 20 or 40 mg/kg) in 37 newborn infants (23 preterm and 14 full term) who already were receiving empirical antibacterial treatment for presumed infection (van den Anker). There were no drug-related adverse events reported. Based on the data generated by this single-dose study, it was concluded that a regimen of 20 mg/kg meropenem every 8 hours would result in adequate meropenem systemic exposure; however, few of these infants were <30 weeks gestational in the first week of life. The second recently completed study supports 20-30mg/kg as the initial doses for younger and more mature infants, respectively. This study included a population PK analysis of meropenem in preterm and term infants (Capparelli et al ICAAC 2006). Of the 37 infants enrolled, 22 were preterm and the mean gestational age was 30 weeks. The preponderance of preterm infants in this study complements the van den Anker study. The population analysis demonstrated an effect of post-conception age where post-conception age is defined as post-natal age (PNA) + gestational age (GA) at birth. Additionally, serum creatinine was correlated with meropenem clearance. The model predicted meropenem dosed in preterm infants at 20-30mg/kg q 8-12hr would maintain serum concentrations above 4 mcg/mL for more than 75% of the dose interval in about 3 quarters of simulated infants.

1.6 Rationale for Initial Dosage Selection and Dose Escalation

Meropenem demonstrates time dependent pharmacodynamics. Clinical antimicrobial effects are observed when concentrations exceed the MIC for at least 30-40% of the dose interval in immunocompetent subjects; and for neutropenic subjects, levels should exceed the MIC for >75% of the dose interval. We consider neonates to be relatively immunocompromised. We

determined the dose needed to provide exposure above MIC of 2 mcg/ml for >75% of the dosing interval in most of the patients, and above MIC of 4 mcg/ml (upper limit of MIC) for >50% of the interval for >90% of patients. We suspect that the inflammatory process and capillary leak associated with necrotizing enterocolitis and bowel perforation may increase the volume of distribution of the drug in the sickest infants. We aim to avoid sub-therapeutic exposure in these infants. The following initial meropenem dosing scheme was predicted to achieve the therapeutic exposure metric in a majority of infants in simulation studies using a population PK model for meropenem in neonates. We will dose escalate if we do not achieve concentrations above the MIC 2 mcg/ml for >75% of the dose interval in at least 90% in any age/dose strata.

Initial Dosing:

Infants <32 weeks

<2 weeks PNA	20 mg/kg Q12
≥2 weeks PNA	20 mg/kg Q8

Infants ≥32 weeks

<2 weeks PNA	20 mg/kg Q8
≥2 weeks PNA	30 mg/kg Q8

2.0 Study Objectives

This study will evaluate the safety, tolerability and PK-PD of meropenem in infants <91 days of age with suspected and complicated intra-abdominal infections.

The specific aims of this trial are:

1. To characterize meropenem single-dose and multiple-dose PK in subjects with suspected and complicated intra-abdominal infections.
2. To characterize the safety profile of meropenem in the treatment of suspected and complicated intra-abdominal infections.
3. To assess collected efficacy data for meropenem for the treatment of suspected and complicated intra-abdominal infections.

3.0 Investigational Plan

3.1 Overall Study Design

This is a multi-center, prospective, pharmacokinetic and safety study of meropenem in infants less than 91 days of age for the treatment of suspected or documented complicated intra-abdominal infections.

The dose of meropenem, stratified by gestational age and post natal age, is predicted to provide therapeutic exposure in the majority of infants. Infants will be enrolled in four GA/PNA strata. Safety will be assessed in real time by the Meropenem Off-Patent Drug Studies (MPODS) Clinical Events Safety Committee and by an independent Data Safety Monitoring Board (DSMB). First dose and steady state meropenem PK will be studied in an interim analysis by GA/PNA group once approximately 12 babies have enrolled in a GA/PNA strata. During interim PK analysis, infants in the GA/PNA group under analysis will continue to be enrolled for ongoing safety evaluation and steady state PK. If the interim PK analysis suggests that the initial dosing does not achieve concentrations more than the MIC 2 mcg/ml for more than 75% of the dose interval in at least 90% of infants then we will plan to dose escalate. We will then enroll 12 infants per group using a higher dose regimen. First dose and steady state meropenem PK will be obtained along with ongoing safety evaluation. Subsequent patient enrollment to final goal of 200 infants will occur in safety group with steady state PK.

1) First dose and steady state meropenem PK will be studied in infants <91 days of age using a population PK design.
2) There will be four GA/PNA groups (see 3.2 below)
3) Approximately 200 infants will be enrolled.
    a. First dose and steady state PK
        i. At least 12 infants enrolled in 4 GA/PNA strata at initial dose (48 infants)
        ii. At least 12 infants enrolled in 4 GA/PNA strata at higher dose if interim PK analysis suggests that exposure target is not met in initial 12 subjects (48 infants)
    b. Safety and steady state PK
        i. Up to 152 additional infants will be enrolled for ongoing safety evaluation and further collection of steady state PK data. These safety/steady state infants will receive initial dose of meropenem unless a determination of dose escalation is made. If dose escalation is warranted then ongoing enrollment in this group will be at higher dose.
4) Investigators are encouraged to provide infants with concomitant aminoglycoside therapy. Use of other antimicrobial agents is discouraged, but may be given per local standard of care

The 200 infants in this trial will receive at least 3 days and no more than 21 days of therapy with meropenem. Infants may be given therapy until the attending physician believes that the infant has had presumptive clinical cure.

3.2 Selection of Study Population

Infants who meet the inclusion/exclusion criteria will be enrolled up and including DOL 90, inclusive. Infants will be enrolled in each of the following groups:

Group 1: GA at birth below 32 weeks - PNA < 2 weeks;
Group 2: GA at birth below 32 weeks - PNA ≥ 2 weeks and < 91 days;
Group 3: GA at birth 32 weeks or older - PNA < 2 weeks;
Group 4: GA at birth 32 weeks or older - PNA ≥ 2 weeks and < 91 days.

3.3 Inclusion Criteria Selection of Study Population

a. Written permission from parent or legal guardian
b. Age younger than 91 days
c. Likely to survive beyond the first 48 hours after enrollment
d. Sufficient intravascular access (either peripheral or central) to receive study drug.

AND ONE OF THE FOLLOWING

e. 1) Physical, radiological, and/or bacteriological findings of a complicated intra-abdominal infection. These include peritonitis, NEC Grade II or higher by Bell's criteria, Hirschsprung's disease with perforation, spontaneous perforation, meconium ileus with perforation, bowel obstruction with perforation, as evidenced by free peritoneal air on abdominal radiograph, intestinal pneumotosis or portal venous gas on abdominal radiographic examination.

OR

2) Possible NEC

OR

3) Otherwise receiving meropenem per local standard of care

3.4 Exclusion Criteria

a. Renal dysfunction evidenced by urine output <0.5 mL/hr/kg over the prior 24 hours
b. Serum creatinine >1.7 mg/dL
c. History of clinical seizures or EEG confirmed seizures
d. Concomitant treatment with another carbapenem (ertapenem or imipenem) at the time of informed consent
e. Any condition which would make the subject or the caregiver, in the opinion of the investigator, unsuitable for the study

3.5 Withdrawal from Study

Infants may be withdrawn from treatment or from the study at any time. Reasons for infant withdrawal from the study include, but are not limited to:

1. Infant's parent or legal guardian chooses to withdraw the infant for any reason
2. AEs, conditions, or intercurrent illnesses that preclude compliance with the protocol, particularly if continuation would pose a risk to the infant's safety
3. Clinical seizure occurring between informed consent and 1st administration of study drug
4. The investigator determines that it is in the infant's best medical interest to be withdrawn.

Detailed reasons for infant withdrawal because of lack of efficacy or because of pre-determined safety concerns are given in the appropriate sections of this protocol. Withdrawn infants will be followed for safety end points to the extent possible.

3.6 Prior and Concomitant Therapy

All antimicrobial agents and all medications received during the 72 hours prior to study administration and for 72 hours following last dose of study drug will be recorded on the appropriate case report form (CRF).

3.7 Assessments

3.7.1 Efficacy Assessments

Limited efficacy data will be obtained. Efficacy data will be based on comparing initial clinical status to clinical status at study Day 28. Initial clinical status will be based on the presenting signs and symptoms of each infant and will be recorded by the local principal investigator (PI) or designee prior to administration of the first dose of study drug . The same physician should record the clinical signs and physical findings on study Day 0 (pre-study drug) and Day 28 in order to derive the efficacy assessments. Success is defined as all of the following:

1) Alive,
2) Negative bacterial cultures from sterile body fluid, and
3) Presumptive clinical cure (details of the presumptive clinical cure are provided below)

Failure will be defined by any of the following:

1. Change in antibiotic therapy while on study drug will be considered a treatment failure except the addition of Gram positive therapy to treat organisms that require it and have been isolated from a non-abdominal source (including CONS, MRSA);
2. Death; or
3. Lack of presumptive clinical cure

The presumptive clinical cure score will be derived by comparing clinical signs and symptoms prior to administration of the first dose of study drug and study Day 28. The clinical, laboratory and radiographic findings are based on the components of the Score for Neonatal Acute

Physiology (SNAP) II and other items listed below. It is acknowledged that the SNAP II has not been validated as a clinical tool beyond the first hours of life, but there is not a clinical tool to predict mortality in serious abdominal infections. The original assessment, efficacy assessment and resulting efficacy interpretation is listed in the following table:

Initial Assessment	Efficacy Assessment	Resulting Efficacy Interpretation and Score
Asymptomatic	Asymptomatic	1
Asymptomatic	Worsening	0
Symptomatic	Worsening	0
Symptomatic	No change	0
Symptomatic	Improved	1
Symptomatic	Asymptomatic	1

If 7 or more of 10 signs receive a score of 1, then the infant will be considered a presumptive clinical cure. The elements of the presumptive clinical score are:

I. Mean blood pressure
II. Temperature
III. PaO_2 (mmHg)/FiO_2
IV. Lowest serum pH
V. Presence or absence of seizures*
VI. Urine output
VII. Cardiovascular inotrope support: Record number and amount of each cardioactive drug
VIII. C-reactive protein (CRP)[#] (prior to study drug, day 3-5, and day 28)
IX. Abdominal girth
X. Findings on abdominal radiograph^

*The presence or absence of seizures will be adjudicated by the MPODS Clinical Events and Safety Committee. The composition, roles and responsibilities of the MPODS Clinical Events and Safety Committee is outlined in the MPODS Clinical Events and Safety Committee charter.

[#]For efficacy assessment, trends in CRP levels will be evaluated on 3 occasions: baseline (72 hours) prior to study drug, between day 3-5, and on day 28 (or at least 7 days after completion of meropenem if day 28 assessment is performed early because infants is nearing discharge). Inability to obtain a CRP level will result in a protocol deviation that will be reported to the study PI but will not disqualify the patient from the study. (see section 5.6)

^The findings on abdominal radiograph will be determined locally.

When there are multiple observations for one aspect of the clinical score recorded at baseline or study Day 28 (e.g., more than one temperature is obtained on Day 28), then the first reading obtained will be used unless the reading is felt by the PI to be spurious and noted as such in the record. Non CRP elements of clinical score that are not otherwise available as part of standard clinical care will be omitted. If the infant is nearing discharge, the score may be recorded prior to study day 28, provided that the infant has been off meropenem for at least 7 days.

3.7.2 Safety Assessments

The collection of safety data is a primary objective of this trial. The safety of meropenem will be a primary focus for monitoring AEs. Safety assessments will include death, seizure documentation, strictures, perforation, wound dehiscence, short gut, development of extended

beta lactamase infection, development of candidiasis, and antimicrobial therapy failure. physical examination, clinical laboratory values and concomitant medications. Vital signs, electrolytes, creatinine, BUN, liver function tests (LFT) and complete blood counts, will be recorded weekly when available per local standard of care. Serious adverse event (SAE) data will continue to be collected for 30 days following completion of study drug administration.

3.7.3 PK Measurements

A population PK approach will be employed. This will include sparse sampling with samples obtained at time intervals rather than at fixed times for assessment of drug concentration. Samples will be no more than 100μL each. Prior to PK sampling (pre study drug assessment), creatinine, BUN, liver function tests (LFT), and urine output over previous 24 hours will be recorded. The complete sampling schedule for assessment of PK parameters is outlined in the PK Appendix. All sample times will be recorded on the appropriate CRF in 24 hour time format. All timing and length of drug infusions before PK sampling is obtained will also be listed on the CRF. Daily weight and all meropenem doses will be recorded on CRF. Infants in each PK cohort will continue to be enrolled to ensure at least 12 infants with at least 3 PK samples around the 1st dose AND 2 samples at steady state.

4.0 Procedures and Study Visits

	Study Day			
PROCEDURE	**0[a]**	**1-27**	**28**	**29 to end of study[a]**
Informed Consent	X			
Abdominal radiographic tests[l]	X	X	X	X
Sterile body fluid cultures[b,c]	X	X	X	X
Abdominal surgical procedures[b]	X	X	X	X
Medical Baseline Conditions	X			
Pertinent Medical History	X			
Physical Exam	X	X	X	
Concomitant Medications[d]	X	X		
Body Weight[e]	X	X	X	
Vital signs, length, head circumference[f]	X	X	X	
Adverse Events[g]	X	X	X	X
Laboratory evaluation[f]	X	X		
CRP[h]	X	X	X	
PK Evaluation[i]		X		
Study drug administration[j]		X		
Clinical Score (see 3.7.1)	X		X	
Efficacy Assessment[k]			X	

a) Day 0 refers to time point prior to start of meropenem but may be the same calendar date as day 1. End of study is 30 days after last administration of study drug
b) Record results from 7 days prior to study drug and 30 days post completion of study drug
c) Record results of sterile body fluid cultures (blood, CSF, Urine, peritoneal fluid) as obtained for clinical care
d) Record from 72 hours prior to first dose and until 72 hours after completion of study drug
e) Assessed prior to first dose and document daily during therapy if available as local clinical care of infant.
f) Assessed prior to first dose and document weekly until 7 days following last dose if available as local clinical care of infant.
g) Record SAEs until 30 days and non serious adverse events until 72 hours following last dose of study drug
h) CRP will be obtained on 3 occasions: 1) within the 72 hours prior to 1st dose of meropenem; 2) between study days 3-5; and 3) on study day 28.
i) Obtain per Appendix 2 and single sample at time of suspicious clinical seizure

j) Treatment for minimum of 3 days and maximum 21 days
k) Obtain at study Day 28; efficacy assessment includes alive, documentation of negative bacterial cultures, and presumptive clinical cure (clinical score elements listed in 3.7.1)
l) Record results from 72 hours prior to first dose and 30 days post completion of study drug

4.1 Procedures Prior to Receipt of First Dose of Study Drug

4.1.1 Parental/Guardian Permission

Prior to the start of any study-related procedure, a signed and dated informed consent and HIPAA authorization must be obtained and documented in the infant's medical record (see Appendix). Once it has been determined that the infant meets all inclusion criteria and no exclusion criteria, the infant will be assigned a subject identification number that will be used on the subject's CRFs and will be considered enrolled. Per inclusion criteria, infants may receive meropenem prior to enrollment.

4.2 Study Drug Administration

4.2.1 Assignment to Therapy Groups

Infants meeting the eligibility will receive meropenem. Concomitant use of an aminoglycoside is suggested. Enrollment and study drug dose will be stratified by GA and PNA as outlined in Sections 1.6 and 3.2. If the infant received meropenem for clinical care within 5 days prior to enrollment date, the first dose kinetics will not be obtained for this study. The infant will be enrolled in the safety-steady-state PK group (see 4.2.5).

After enrollment information for the eligible infant (demographics, stratification criteria, center, etc.) is provided, the dosage assignment and subject number will be allocated. If an infant is assigned a study drug and a number, but does not receive study drug, the subject number will not be used again. The reason for not dosing the subject will be noted on the CRF.

The BPCA-CC will provide instructions for the investigator to obtain each infant's study drug assignment and PK sampling schedule in a timely manner prior to the administration of study drug. The pharmacist will provide the study drug for infusion according to the dosage group.

4.2.2 Dispensing of Study Drug

Study drug will be distributed to the sites by the BPCA-CC or designee. The pharmacist at each site will prepare and dispense the study drug.

Study drug will be dispensed by the pharmacy in appropriate size syringes and administered via a syringe pump at a rate calculated based on the infants' body weight in kilograms (kg) per local standard of care, but with a target of infusing the product over 30 minutes. The pharmacy will supply study syringes wrapped in amber plastic to protect the contents from light. A new bottle of study drug should be used for every dose.

The compatibility of meropenem with other drugs has not been established. Meropenem should not be mixed with or physically added to solutions containing other drugs. Infusion vials of meropenem will be reconstituted and stored per the package insert and local pharmacy requirements. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

4.2.3 Treatments Administered

Meropenem may be administered concomitantly with compatible medications. An in-line filter is not appropriate. The 30 minute infusion must be rate controlled by using appropriate infusion (syringe) pumps.

Dosing and administration of other antimicrobial therapy (e.g., an aminoglycoside) will be administered per local standard of care at the discretion of the infant's neonatologist. If there is a delay in the study drug shipment, sites may use open-label meropenem to protect the safety of the patient.

4.2.4 Treatment Compliance

Treatment compliance will be evaluated by review of information documented on study drug administration and drug accountability forms.

4.2.5 Dosing for infants receiving meropenem per local standard of care

Infants enrolled that were receiving meropenem per local standard of care prior to study entry will be enrolled in the safety-steady state PK group because 1st dose levels will be impossible to obtain. Only steady state PK samples will be drawn (per the MPODS protocol). The infants will continue to receive meropenem at the dosing administered prior to enrollment in the study if the dose is equal to or greater than the dose indicated by MPODS protocol for the infant's GA/PNA.

For example: An infant born at 34 weeks gestation and 4 weeks post natal age has been receiving meropenem at a dose of 40 mg/kg q8 hours and is consented for the study. Based on the open study group, the infant should receive meropenem (30 mg/kg q8 hours): however, the infant will continue to receive 40 mg/kg q8 hours per the local standard of care. Had the same infant (EGA 34 weeks; PNA 4 weeks) been receiving 20 mg/kg q8 hours, the dosing should be increased to 30 mg/kg q8 hours to comply with minimum MPODS protocol dose.

4.3 Protocol Deviations

When a deviation from the protocol is deemed necessary for an individual infant, the investigator or other responsible physician must contact the MPODS PI or BPCA-CC clinical monitor immediately, unless a delay would endanger the subject, so that a timely decision can be made as to whether or not the infant should be enrolled or continue in the study. The deviation from the protocol will be authorized only for that particular infant. A description of the departure from the protocol and the reason(s) for it must be recorded on the appropriate CRF (for PK sampling deviations) or the provided protocol deviation logsheet. Additionally, sites will adhere to local IRB reporting rules for protocol deviations..

5.0 Safety

Safety assessments will include seizure documentation (including correlation of serum meropenem level and seizures), physical examination, and clinical laboratory values as available per standard local care including LFTs, renal function, blood counts and microbiology cultures of sterile body fluids to track nosocomial infections (by pathogen).

5.1 Safety First Plan

The protocol will rely on three mechanisms for safety:

1. The DSMB whose role is outlined below and in the BPCA-CC DSMB charter;

2. AE and SAE reporting mechanisms in accordance with FDA guidance outlined below
3. The active, daily, real time oversight of the MPODS Clinical Events and Safety Committee

5.1.1 Data Safety and Monitoring Plan

The BPCA-CC will establish the Data Safety and Monitoring Plan (DSMP) in compliance with NIH policies for the protection of human subjects in clinical studies. The BPCA-CC DSMP outlines procedures for reporting SAEs and AEs of Special Interest to the BPCA-CC and dissemination of this information from the BPCA-CC to the DSMB and MPODS Clinical Events and Safety Committee.

5.1.2 Data and Safety Monitoring Board

An independent DSMB established in accordance with the "NIH Policy for Data and Safety Monitoring" will monitor the conduct of the trial for performance (e.g., recruitment, flow and quality control of data, adherence to the protocol), patient safety, and efficacy. The DSMB may review the data at any time. At any time and for any reason, the DSMB may recommend to the NICHD Project Officer that the trial be interrupted or discontinued.

5.1.3 AEs

The AEs of Special Interest (1 and 2 below) not otherwise explained by the patient's underlying illness and all SAEs will be submitted in writing (via fax or electronic communication) to the BPCA-CC medical monitor within 24 hours of occurrence. The BPCA-CC will then notify the MPODS PI, MPODS Clinical Events and Safety Committee and the DSMB within one working day after receiving the report from a clinical site. Local IRB guidelines will also be followed.

AEs to be submitted to the BPCA-CC medical monitor within 24 hours of occurrence:

1. Level 2 laboratory AEs (Refer to Table 1) not otherwise explained by the subject's underlying illness
2. Seizures judged not otherwise explained by the subject's underlying illnesses including:
    a. IVH
    b. Meningitis
    c. Electrolyte abnormality
    d. Genetic/metabolic disorder
    e. Drug withdrawal
    f. Hypoxia-ischemia
    g. Cerebral anomalies
3. All SAEs

Table 1: Laboratory AEs of Special Interest

Parameter	Level 1	Level 2
Direct bilirubin		> 5 mg/dL
Indirect bilirubin		>15 if <36 weeks adjusted GA >20 if >36 weeks adjusted GA
AST	Increase 5* (baseline)	Increase 10* (baseline)
ALT	Increase 5* (baseline)	Increase 10* (baseline)
Creatinine	Doubling of baseline serum creatinine and > 1.5 mg/dL	> 2.5 mg/dL

When clinical seizures or seizure-like activity occurs not otherwise explained by the patient's underlying illness, the local PI (or their designee) will record the findings on the CRF. EEG's, if obtained per local standard of care, will be evaluated. The local PI will obtain a copy of the EEG, preferably in digital format, remove all patient identifiers except study ID, and submit as source documentation for the seizure or seizure like activity. These digital documents and the CRF will be presented to the MPODS Clinical Events and Safety Committee pediatric neurologist. The neurologist will make a final determination of whether or not the infant has had a seizure or seizure like activity.

If seizures occur while on therapy, obtain 100 ul of blood (if possible) to document meropenem level at time of seizure. When possible, obtain up to 2 additional samples, each at least 24 hours apart, during infant seizure activity. Scavenged samples whenever possible are appropriate during infant seizure activity. Time of sample collection will be recorded on CRF. These samples will be sent to the central lab with the other PK samples from the infant.

5.1.4 MPODS Clinical Events and Safety Committee

The roles and responsibilities of the MPODS Clinical Events and Safety Committee are outlined in the MPODS Clinical Events and Safety Committee charter. If interim PK analysis on 12 subject PNA/GA groups reveals that a higher dose is needed to reach the exposure target, then the MPODS Clinical Events and Safety Committee will review AEs and determine if dose escalation can occur by applying the dose escalation safety rules outlined below.

The dose escalation safety rules are to be applied to each GA/PNA group (1-4) separately, thus allowing dosing in each age cohort to progress independently.

1. Escalation of dosage may occur if no more than 3 subjects (or 25% of the group if the size of the group is >12) in an age group develop any of the following:
    a. Level 2 AEs judged by the MPODS Clinical Events and Safety Committee to be related to meropenem
    b. Seizures judged by the MPODS Clinical Events and Safety Committee to be related to meropenem
    c. SAEs that are judged by the MPODS Clinical Events and Safety Committee to be related to meropenem
2. DO NOT escalate dosage if > 3 subjects (or > 25% of the group if the size of the group is >12) in an age group develop any of the following:
    a. Level 2 AEs (defined below) judged by the MPODS Clinical Events and Safety Committee to be related to meropenem
    b. Seizures judged by the MPODS Clinical Events and Safety Committee to be related to meropenem
    c. SAEs that are judged by the MPODS Clinical Events and Safety Committee to be related to meropenem

5.1.5 PK Interim Analysis for Possible Dose Escalation

After obtaining single and steady-state PK samples from approximately 12 infants in each GA/PNA cohort, we will determine if the dose used leads to the pharmacodynamic target exposure. From the PK interim analysis, we will dose escalate if we do not achieve concentrations >2 mcg/ml for >75% of the dose interval in at least 990%in any GA/PNA group (see section 1.6)(Pfaller 1997, Benjamin 2004). We will escalate dosing based on this analysis once safety has been confirmed as described in section 5.1.4. The decision to escalate meropenem dosage will be carried out independently for each GA/PNA group.

5.2 Adverse Events

5.2.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence such as a sign(s), symptom (s), and/or laboratory finding(s) concurrent with the use of a drug in humans. AEs include worsening of any baseline symptoms. The event may/may not necessarily have a causal relationship with the administration of the drug. AEs may be reported by the subject, or detected by the investigator, or other competent observer. The investigator will also evaluate any change in laboratory values. If the investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the laboratory value abnormality is consistent with a current diagnosis, it may be documented accordingly.

5.2.2 Reporting period

AEs will be recorded from the time of informed consent until 72 hours following the last dose of study drug for non SAEs and until 30 days after the last dose of study drug for SAEs. Any AE that occurs between the time informed consent is obtained and the initial dose of study, that is considered related to a protocol specified procedure, must be reported.

5.2.3 Procedures for assessing, recording and reporting AEs

Throughout the duration of the study, the investigator will closely monitor each subject for clinical evidence of drug intolerance and monitor all clinically obtained laboratory values for laboratory evidence of AEs. AEs not explained by the infant's underlying illness which occur during the course of the study will be reported in detail on the appropriate CRFs and followed until resolution or until it becomes stable. All SAEs will be reported to BPCA-CC within 24 hours.

The description of the AE will include description of event, start date, stop date, intensity, if it was serious, and relationship to the study drug. The investigator must verify this information.

The intensity or severity of AEs will be graded as follows:

- **Mild** - awareness of sign or symptom, but easily tolerated. Not expected to have a clinically significant effect on the subject's overall health and well-being. Not likely to require medical attention
- **Moderate** - discomfort enough to cause interference with usual activity or affects clinical status. May require medical intervention
- **Severe** - incapacitating or significantly affecting clinical status. Likely requires medical intervention and/or close follow-up

AEs that increase in intensity will be recorded with a stop date on the AE CRF of the milder AE equal to the date that the condition worsened. A new AE with a start date equal to the date of worsening will then be reported. AEs that decrease in severity need not be reported in this way. The start date will be the date entered above and the date of resolution should be reported as the stop date.

The Investigator is responsible for assessing relationship to study medication using the following definitions:

- **Not related**: An AE that is due to a pre-existing illness or use of another drug, and is not related to the study drug.

- **Possibly related**: An AE that has little or no relationship to the study drug and there exists a more likely alternative cause.
- **Probably related**: An AE that is likely to be related to the administration of the study drug and an alternative cause less likely when compared to the study drug.
- **Definitely Related**: An AE that has a strong temporal relationship to the study drug. AE will recur with continued or repeated use of the study drug, and another cause is unlikely or less likely.

5.2.4 Follow-up of AEs

AEs will be followed until resolution or until stability is reached using good clinical practices.

5.3 Serious Adverse Event

A SAE is defined (21 Code of Federal Regulations part 312.32) as those AEs, which meet any of the following serious outcome criteria:

- Is fatal
- Is life-threatening, meaning, the subject was, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death;
- Is a persistent or significant disability/incapacity, i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions;
- Requires or prolongs inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an important medical event, based on appropriate medical judgment, that may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the other outcomes above.

5.3.1 Procedures for assessing, recording and reporting SAEs

All SAEs must be reported by facsimile or electronic transmission to BPCA-CC within 24 hours after the onset of the SAE (or the awareness of the investigator of the event). The BPCA-CC then notifies the MPODS PI, MPODS Clinical Events and Safety Committee and the DSMB of SAE within one working day after receiving the report from a clinical site. In addition, a clinical site must report a death or life-threatening event by telephone as soon as possible and within 24 hours to the BPCA-CC.

A SERIOUS ADVERSE EVENT FORM must be completed and signed by the site investigator. All SAEs must also be entered into the AE CRF (select "serious").

The FDA requires that all SAEs that are unexpected and potentially related to the study medication must be reported to the FDA in writing within 15 calendar days of notification of BPCA-CC. SAEs that are unexpected and related to study drug that meet the criteria for death or immediately life-threatening also require BPCA-CC to notify the FDA by telephone, facsimile transmission or in writing as soon as possible but no later than seven calendar days, with a follow-up written report within 15 calendar days. BPCA-CC will prepare an expedited report for the FDA and copies will be distributed to all site investigators. Expedited reports will be placed in the Study Binder by the investigator upon receipt. The investigators will also forward a copy of all expedited reports to their local Investigational Review Boards in accordance with local guidelines .

5.3.2 Follow-up of SAEs

The investigator must complete and submit a follow-up SAE form when important follow-up information (diagnosis, outcome, results of specific investigations, etc.) becomes available after submission of the initial form. Follow-up forms should be submitted according to the same process used for reporting the initial event as described above (i.e., within 24 hours of knowledge). All SAEs and AEs of Special Interest will be followed until resolution, stabilization or 30 days after the last subject is enrolled, whichever occurs, first. The investigator will be responsible for reporting SAEs to the local IRBs in accordance with local guidelines.

5.4 IRB summary safety reports

As required by the NIH "Guidance of Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials," the DSMB's summary safety reports will provide feedback at regular and defined intervals to the Institutional Review Boards (IRBs). After each meeting of the DSMB, the executive secretary will send a brief summary safety report to each investigator. The report will document that a review of data and outcomes across all centers took place on a given date and will summarize the Board's review of the cumulative adverse experiences reported from all participating sites without specific disclosure by treatment arm. It will also inform investigators of the study the Board's conclusion with respect to progress or need for modification of the protocol. The clinical site investigators are required to transmit the report to their local IRB as soon as they are received.

5.5 Seizures

Seizures will be closely monitored throughout the trial. The presentation of a seizure can be subtle such as ocular deviation, sucking and lip smacking movements, swimming or 'rowing' or 'bicycling' movements of limbs. They can be tonic/clonic, localized, multifocal, or generalized. They may also be diagnosed by EEG. If seizures (or possible seizure like activities) are present, they are to be recorded on the CRF. Assessment of seizure activity prior to enrollment, at enrollment, while on study drug and up to 30 days post study drug administration are to be recorded on the CRF.

If seizures occur while on therapy, obtain 100 ul of blood (if possible) to document meropenem level at time of seizure. When possible, obtain up to 2 additional samples, each at least 24 hours apart, during additional infant seizure activity. Scavenged samples whenever possible are appropriate during infant seizure activity. Time of sample collection will be recorded on CRF. These samples will be sent to the central lab with the other PK samples from the infant.

The CRF will have a seizure documentation page for every infant thought to have a seizure or seizure-like activity by the local site PI not explained by the infant's underlying illness. When clinical seizures or seizure-like activity occurs, the local PI (or their designee) will record the findings on the CRF. EEG's, if obtained per local standard of care, will be evaluated. The local PI will obtain a copy of the EEG, preferably in digital format, remove all patient identifiers except study ID, and submit as source documentation for the seizure or seizure like activity. These digital documents and the CRF will be presented to the MPODS Clinical Events and Safety Committee pediatric neurologist. The neurologist will make a final determination of whether or not the infant has had a seizure or seizure like activity. The decision by the MPODS Clinical Events and Safety Committee pediatric neurologist will be used to determine whether dosing level is to be advanced in an age group (Centrally Diagnosed Seizure).

Infants with seizures or seizure-like activity will be characterized in four components:

1) Locally Diagnosed Clinical Seizure (yes/no),
2) Locally Diagnosed EEG-confirmed Seizure (yes/no),
3) Centrally Diagnosed Clinical Seizure (yes/no),
4) Centrally Diagnosed EEG-confirmed Seizure (yes/no)

5.6 Blood Volume for PK and Safety Laboratory Tests

Blood samples will be minimized by:

1. Hematology and chemistry laboratory measures will be recorded from laboratories drawn as standard of care and will not be drawn strictly for purpose of this study.
2. No more than 2cc/kg will be obtained for study purposes. First priority for blood acquisition is PK samples (up to 0.7cc of blood). Second priority is CRP levels.
3. CRP levels will be obtained from the patients on 3 occasions: baseline (72 hours) prior to study drug, between days 3-5 and on day 28 of the study. CRP levels can be obtained from residual blood in clinical laboratory if less than 12 hours from time of sample collection. Inability to obtain CRP levels will result in a protocol deviation that will be reported to the MPODS PI but will not disqualify the patient from the study.
4. A limited PK sampling scheme will be employed such that no more than a total of 0.7 mL of blood (7 samples) is obtained from each subject for PK analysis.

6.0 Procedures by Visit

6.1 Pre-Study Drug Administration Procedures (Day 0)

The following procedures will be completed prior to the administration of study drug:

a. Review of Inclusion/Exclusion Criteria prior to infant enrollment
b. Obtain signed and dated informed consent/HIPAA consent.
c. Collect demographic data and medical/surgical history
d. Perform a complete physical examination
e. Obtain and record vital sign measurements, length and head circumference
f. Obtain and record infant weight in grams and medication dosing weight for calculation of appropriate study drug dose if different from actual weight
g. Record results from hematology and serum chemistry labs. Hematology assays will include: hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, and platelet count. Serum chemistry will include glucose, creatinine, blood urea nitrogen, aspartate transaminases (AST), alanine transaminase (ALT), alkaline phosphatase, total and direct bilirubin, sodium, potassium, chloride, calcium, magnesium, total protein, and albumin laboratory evaluations. If these labs have been obtained within 72 hours prior to enrollment in accordance with local standard of care, the results may be used for the baseline values for the study. Use the laboratory values closest to enrollment if there have been multiple tests. **Do not collect additional samples for the purposes of this study**.
h. Record results of sterile body fluid cultures (blood, urine, CSF, peritoneal fluid) obtained as standard clinical care in the 1 week prior to study drug administration. Record Urine cultures only if obtained by sterile catheterization or suprapubic aspiration.
i. Document antimicrobial agents and concomitant medications in the 72 hours prior to study drug administration.
j. Document prior abdominal surgical procedures in the 1 week prior to study drug administration.
k. Document confirmed serious or suspected intra-abdominal infection
l. Document clinical signs of intra-abdominal infection

m. Document the results of abdominal XRAY in 72 hours prior: including A-P and lateral (either cross-table or left lateral decubitis) plain films. This will serve as the 'baseline' film set for the infant.
n. Record the presumptive clinical cure score initial assessment (10 elements of clinical score): mean blood pressure; temperature; PO_2 (mmHg)/FiO_2; lowest serum pH (if obtained per standard of care); presence or absence of seizures; urine output; cardiovascular inotrope support (record name and dose of each cardioactive agent); CRP (Obtain 1 CRP in the 72 hours prior to enrollment. If multiple CRPs are collected as part of standard of care during this time, record the value closest to the 1st dose of meropenem); abdominal girth; and findings on abdominal XRAY (if obtained per standard of care). If more than one clinical score element result is obtained on Day 0 prior to study drug administration, record the results of the first study obtained that day. Except for CRP, clinical assessments not obtained as local standard of care will not be recorded.
o. Assess and record AEs between the time informed consent is obtained and the initial dose of study drug that are considered related to a protocol specified procedure.

6.2 Procedures During Study Drug Administration

The following procedures or evaluations will be performed during the treatment phase and the data recorded as indicated. The first dose of drug defines the beginning of study Day 1

6.2.1 Study Days 1-27

a. Record study drug timing of infusion before the PK samples are obtained—this includes start/stop times of infusion, time (24 hour clock) of infusion, and amount given
b. Assess and record AEs from the time of the first dose of study drug through 72 hours following the last dose study drug.
c. Record weight of the patients daily during meropenem administration
d. Record all meropenem drug administration: date, start time, dose: minimum of 3 days and maximum of 21 days.
e. Dosing adjustments should be made on Study Days 7, 14, 21 based on change in PNA or new dosing weight to be determined by the infant's physician
f. Record all concomitant medications administered
g. Collect blood for PK analysis (Schedule provided in Appendix). PK samples are not to be drawn from the lumen of the catheter through which meropenem has been administered. Samples may be collected through the lumens of other catheters, venous sampling, arterial sampling, or capillary heel-sticks.
h. Record result for clinical laboratory assessments obtained per local standard of care (listed in 6.1 g) one time weekly while on study drug (day 1-7, day 8-14, day 15-21, day 22-28) while on therapy and up until one week after therapy completion. These assessments include CBC, AST, ALT, bilirubin (total and direct), creatinine, electrolytes, and BUN. **Do not collect additional samples for the purposes of this study**.
i. Record the results of cultures from sterile body fluids (blood, urine, CSF, peritoneal fluid, or any other sterile body fluid) as obtained per standard of care up to 30 days after last study drug (consistent with section 6.3).
j. Record any abdominal surgical procedures up to 30 days after last study drug (consistent with section 6.3).
k. Record results of any abdominal radiological examinations (e.g., XRAY, ultrasound, CT scan, MRI) up to 30 days after last study drug (consistent with section 6.3).

l. If seizures occur while on therapy, obtain 100µL of blood (if possible) to document meropenem level at time of seizure. These will be sent to the central lab with the other PK samples from the infant. An additional 2 samples, each at least 24 hours apart, during additional infant seizure activity may be obtained. Scavenged samples whenever possible are appropriate during infant seizure activity.
m. Obtain 1 CRP between study Days 3 and 5. If CRPs are collected as part of standard of care between days 3 and 5, these are to be recorded on the appropriate CRF. If more than one CRP is collected on a calendar day, record the first CRP obtained.

6.2.2 Study Day 28: Documentation of Clinical Response

If the infant is nearing discharge, the score may be recorded prior to study day 28, provided that the infant has been off meropenem for at least 7 days.

Record efficacy assessment variables: (3.7.1)

1) Alive
2) Negative bacterial cultures from sterile body fluid
3) Presumptive clinical cure

Record the following and compare to initial evaluation

I. Mean blood pressure
II. Temperature
III. PaO_2 (mmHg)/FiO_2
IV. Lowest serum pH
V. Presence or absence of seizures
VI. Urine output
VII. Cardiovascular inotrope support: Record number and amount of each cardioactive drug
VIII. CRP
IX. Abdominal girth
X. Findings on abdominal radiograph

6.3 Procedures following Study Drug Administration

1. Record concomitant medications for 72 hours after the last dose of study drug.
2. Record the following information for 30 days following the last dose of study drug:
   a. Assess and record SAEs
   b. Record all positive microbiology cultures from sterile body fluids
   c. Record any abdominal surgical procedures and surgical finding
   d. Record any results from abdominal radiological examinations (e.g., XRAY, ultrasound, CT scan, MRI) performed
   e. Record presence or absence of strictures, peritoneal abscesses

7.0 Administration

7.1 Trial Termination

The NICHD, the BPCA-CC, the PODS PI and the Duke Clinical Research Institute (DCRI) will monitor the progression of the trial. Investigator and site participation in the study may be terminated by the PODS PI if there is evidence of an investigator failing to maintain adequate clinical standards or evidence of an investigator or staff failing to comply with the protocol.

7.2 Data Safety and Monitoring Board

To ensure that the welfare of trial subjects receives appropriate consideration, an independent DSMB has been organized by the BPCA-CC to review relevant safety and/or efficacy data during the course of the trial. The DSMB may recommend discontinuation of the study, or modifications to the study protocol for safety reasons. The DSMB charter is available from the BPCA-CC.

7.2.1 Meropenem Escalation

If interim PK analysis reveals that dose escalation is necessary to achieve target exposure then the MPODS Clinical Events and Safety Committee will be responsible for determining if dose escalation can occur based on review of the safety data as described in section 5.1.4. Escalation can occur in one GA/PNA group irrespective of enrollment or trial progression in the other groups.

7.3 Investigational Product

7.3.1 Rationale for Investigational Product

Meropenem will be used as empirical therapy. It provides excellent coverage for most of the bacterial pathogens in isolated from infants in the nursery. It does not provide coverage for methicillin resistant *S. aureus* (MRSA), most coagulase negative staphylococci, or for ampicillin resistant *Enterococcccus*, but these organisms have limited additional mortality in the nursery (Benjamin 2004).

An aminoglycoside is suggested as additional coverage for additional empirical Gram Negative Rod (GNR) coverage. Its administration is based on the uncertainty of the efficacy of the proposed dosages of meropenem. This will ensure that all infants have therapeutic empirical antimicrobial therapy for GNR organism, and that many infants will likely have double coverage for empirical GNR coverage. An aminoglycoside does not provide coverage for MRSA, most coagulase negative staphylococci, or for ampicillin resistant *Enterococcccus*.

GNR coverage: Will be guaranteed by an aminoglycoside and bolstered by meropenem.

Gram Positive Cocci (GPC) coverage: Will likely be provided by meropenem except for methicillin resistant organisms. Attributable mortality in the nursery from these organisms approaches 0. (Benjamin 2004).

Anaerobic coverage: Some coverage will likely be provided by meropenem. Benefits of empirical therapy with anti-anaerobic coverage are not known (Faix et al) and definitive therapy may be added per local standard of care if the infant has an anaerobe isolated from sterile body fluid or the abdomen perforates.

Antifungal coverage: May be provided per local standard of care

7.3.2 Description of Investigational Product

Meropenem is a pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. It is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S \cdot 3H_2O$ with a molecular weight of 437.52.

7.4 Storage and Disposition of Supplies

The clinical supplies will be stored at controlled room temperature from 15°- 30°C and protected from light in its carton until used. Investigational products are for investigational use only, and are to be used only within the context of this study. Study drug must be maintained under adequate security.

7.5 Drug Accountability

The investigator or his/her designee will verify that study drug supplies are received intact and in the correct amounts. The investigator or his/her designee will document this verification by signing and dating the appropriate shipment request/receipt document. An accurate inventory of study drug will be kept by the site. An overall accountability of the study drug will be performed and verified by the clinical research associate (CRA) throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for, and disposed at the study site according to the institution's standard operating procedures (SOPs) following review by the CRA. The investigator agrees not to supply study medication to any persons not enrolled in the study.

8.0 Statistical Methods

8.1 General Considerations of the Statistical and Analytic Plans

The primary objectives of this analysis are to assess the PK and safety of meropenem in young infants.

8.2 Definitions and Populations for Analysis

All infants who receive meropenem will be analyzed. These infants will comprise the population for the safety analysis, and if any PK samples are obtained, their blood will be evaluated in the PK analysis. These infants who have efficacy measurement at Day 28 will also be evaluated for clinical (efficacy) response.

8.3 Demographics

Descriptive statistics such as number of observations, mean, median, 95% confidence interval, standard deviation, standard error, minimum, and maximum will be presented by dosage group for continuous variables (such as age, weight, etc). Other descriptive statistics such as counts, proportions, and/or percentages will be presented by dosage group to summarize discrete variables (such as race, sex, success rates, mortality rates, etc.).

The number of infants completed, and discontinued early from study, and the reasons for discontinuation, will be summarized by dosage. Demographic and baseline characteristics will be summarized by group and dosage. Variables include race, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized in terms of number of days of dosing, and reasons for final discontinuation of study drug.

8.4 Safety

The number and percentage of infants having treatment-emergent AEs will be tabulated, with a breakdown by group. Descriptive statistics will be provided for clinical chemistry and hematology data, including change from baseline. All subjects who received at least one dose of study product will be included in the safety analyses. AEs will be summarized and tabulated by severity, and relationship to therapy. Deaths and premature termination will be tabulated and summarized. Changes in laboratory parameters will be tabulated and summarized. Laboratory data, such as hematology and serum chemistry data will be tabulated by dosage and age group. Summary statistics for changes from baseline will be presented. AEs will be summarized in tabular form by dosage and age group.

Continuous laboratory measurements will be described at each visit using univariable descriptive statistics (mean, median, etc.); observed values and changes from baseline will be summarized. Lab tests reflective of liver toxicity (e.g., ALT, AST) will be further summarized in

terms of the most extreme values and largest changes from baseline (in the appropriate direction) observed from start of study drug through the end-of-therapy lab. Vital signs and physical exam results will be listed.

Key safety endpoints that will be evaluated in the final analysis include: Death, seizures, strictures, perforation, wound dehiscence, short gut, development of extended beta lactamase infection, development of candidiasis, and antimicrobial therapy failure. The key safety endpoints, the proportion expected to develop the endpoints, and the 95%CI are presented in the table below. The proportion of infants affected and 95% CI for each key safety endpoint will be reported. Safety assessments will also include the tracking standard laboratory assessments of hematologic liver and renal function. Assessments will also include growth parameters (weight, length, and head circumference). Strictures will be defined as previously described (Faix 1988).

Analysis of Seizure: Infants with seizures or seizure-like activity will be characterized in four components:
1) Locally Diagnosed Clinical Seizure (yes/no),
2) Locally Diagnosed EEG-confirmed Seizure (yes/no),
3) Centrally Diagnosed Clinical Seizure (yes/no),
4) Centrally Diagnosed EEG-confirmed Seizure (yes/no)

The proportion of infants in each dosage will be compared. We will derive point estimates and 95% CI for each category. Although estimates for each category will be provided and compared, the definitive categorization of seizure will reside with the MPODS Clinical Safety Committee pediatric neurologist. The neurologist will assess the four components listed above and will make a final 'yes/no' call as to whether or not the infant had seizure.

Safety Table: The key endpoints, applicable sample size, expected proportion of population expected to reach safety endpoint, and subsequent expected 95% confidence intervals are presented. This table presents the 95% CI based on a sample size of 48 infants. The number of infants expected in each dosage of meropenem

Safety Endpoint	Expected Proportion	95% CI
Death	20%	0.10, 0.35
Seizures	2%	0.00, 0.11
Strictures	2%	0.00, 0.11
Antimicrobial Failure	45%	0.31, 0.61
Perforation once enrolled	5%	0.01, 0.14
Short bowel syndrome	5%	0.01, 0.14
Development of ESBL infection	2%	0.00, 0.11
Development of candidiasis	10%	0.03, 0.23

8.5 Pharmacokinetics

The complete PK analysis plan will be presented with the final statistical analysis plan (SAP). The following PK parameters will be estimated:

1. Plasma clearance
2. Volume of distribution
3. Cmax, Tmax, AUC_{0-T}, (at steady state), Ke and $t_{1/2}$
4. $AUC_{0-\infty}$ (estimated from the 1^{st} dose)

The PK parameters and MIC will be used to estimate pharmacodynamic parameters of exposure (time above MIC). For PK analysis, using sparse sampling PK parameters will be estimated for the following cohorts:
Group 1: GA at birth below 32 weeks - PNA < 2 weeks;
Group 2: GA at birth below 32 weeks - PNA ≥ 2 weeks and < 91 days;
Group 3: GA at birth 32 weeks or older - PNA < 2 weeks;
Group 4: GA at birth 32 weeks or older - PNA ≥ 2 weeks and < 91 days.

The plasma concentrations-time profiles of meropenem will be presented in tabular and graphical form by subject, age cohort, and dosage level. The relationship between plasma concentrations and/or PK parameters with demographic factors (weight, sex, age and race), disease severity, toxicity and co-administered medications will be investigated. Analysis of potential relationships between drug and exposure in subjects and the resulting efficacy and/or safety response will be conducted. The exact time and date of sample collection and the dosing history information will be recorded on the appropriate CRF.

8.6 Efficacy

An efficacy assessment will be assessed 28 days after first dose of study drug. Success will be defined by all of the following: Alive and negative bacterial cultures (if obtained) from normally sterile body fluids, and presumptive clinical cure score ≥7. Failure will be defined by any of: Change in antibiotic therapy while on study drug will be considered a treatment failure except the addition of Gram positive therapy to treat organisms that require it, or death, or lack of presumptive clinical cure. This study is not powered to determine efficacy. These data will be used in assessing the feasibility of a potential efficacy study.

8.7 Sample Size

The sample size is designed to assess single and multiple dose PK of meropenem in young infants.

9.0 Ethics

9.1 Ethical conduct of the trial

This study will be conducted according to the protocol, the applicable FDA and HHS Code of Federal Regulations, Good Clinical Practice, the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for Good Clinical Practice. It will also adhere to the ethical principles outlined in The Belmont Report.

9.2 Institutional Review Board

Institutional review boards must be constituted according to the applicable State and Federal requirements of each participating site. The investigators and staff of this study and the IRB of each participating institution will rigorously monitor research data to ensure the safety of research subjects, and will protect the privacy and confidentiality of all study subjects.

This protocol must be submitted to appropriate IRBs and their written unconditional approval obtained and submitted to BPCA-CC before commencement of the study. Investigators must also inform IRBs of all subsequent protocol amendments. Verification of IRB unconditional approval of the protocol and the written parental/guardian permission form will be transmitted to BPCA-CC prior to shipment of investigational drugs (if BPCA-CC distributes the drug). This approval must refer to the study by exact protocol title and number, identify documents

reviewed, and state the date of review. All correspondence with the IRB should be filed by the investigator.

Institutional review boards must be informed by investigators of all serious or unexpected AEs occurring during the study that are likely to affect the safety of the subjects or the conduct of the study.

9.3 Informed consent and assent

The principles of informed consent in the current edition of the Declaration of Helsinki should be implemented before protocol-specified procedures are carried out. Informed consent will be obtained and documented in accordance with U.S. 21 CFR Part 50.25, §§ 116, 117 and 408 of 45 CFR Part 46 and all other applicable regulatory requirements.

Prior to any study procedures being performed, the investigator or his/her designee will inform the subject's legally authorized representative (e.g., parent, guardian) of all aspects pertaining to study participation.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB. The subject's legally authorized representative (parent or guardian) must be given ample opportunity to inquire about details of the study.

The description of the study procedures will include the purpose of the research and procedures, risks and benefits of the research, alternative procedures, confidentiality, legal rights, parental or guardian permission, the contact person and phone number if there are any questions, and the voluntary nature of participation. It will be emphasized that participation is voluntary and participants may withdraw from the study at any time without any effect on standard care. The investigator or his/her designee, and the subject's legally authorized representative must both sign and date the informed permission form. An original signed informed permission form will be retained in the site study records. The subject's legally authorized representative will receive a copy of the signed and dated informed permission form and a copy of the signed assent (if applicable).

The parental/guardian permission form generated by the investigator with the assistance of BPCA-CC must be approved (along with the protocol) by the IRB and be acceptable to the Steering Committee. Permission forms must be in a language fully comprehensible to the subject's legally authorized representative. Permission shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject's legally authorized representative.

The written parental/legal guardian permission document will embody the elements of informed consent as described in the Declaration of Helsinki, the Code of Federal Regulations, and the ICH Guidelines and will comply with local regulations. This form may be read to the subject's legally authorized representative, but, in any event, the investigator shall give the representative adequate opportunity to read it before it is signed and dated.

Permission must be documented by the dated signature of the subject's legally authorized representative. The signature confirms the permission is based on information that has been understood. Each signed permission form must be kept on file by the investigators for possible inspection by BPCA-CC, Regulatory Authorities, and NICHD or its designees.

9.4 Protection of personal health information

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials and the subject's study number. The investigators will agree to maintain records identifying the subjects enrolled in the study, which will be used for the purpose of long-term follow-up.

Investigators at each study site will be responsible for insuring compliance with the Privacy Rule, a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA), in accordance with the investigator's institution policy. The Privacy Rule establishes the right of a research subject or subject's legally authorized representative to authorize an investigator to use and disclose subject's personal health information (PHI) for research purposes. This requirement is in addition to the informed consent and assent to participate in the study. A valid Privacy Rule Authorization is a subject's or subject's legally authorized representative signed permission that allows an investigator to use or disclose the subject's PHI for the purposes, and to the recipient or recipients, as stated in the Authorization. The signed Authorization must be retained by the investigator for 6 years from the date of creation or the date it was last in effect, whichever is later.

Authorization can be combined with an informed permission. Whether combined with an informed permission or separate, an Authorization must contain the following specific core elements and required statements stipulated in the Privacy Rule.

9.4.1 Authorization core elements

a. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner
b. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure
c. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure
d. A description of each purpose of the requested use or disclosure
e. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository)
f. Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided

9.4.2 Authorization required statements

a. A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
b. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on
c. Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable
d. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient

Authorization must be written in plain language and contain the core elements and required statements, and a signed copy must be provided to the individual signing it if an investigator itself is seeking the Authorization. An Authorization obtained for the study need not have a fixed expiration date or state a specific expiration event, the form can list “none” or the “the end of the research project.”
Participant or participant’s legally authorized representative has the right to revoke the Authorization, in writing, at any time.

10.0 Source Documents and Case Report Form Completion

10.1 Source documents

Source documents are defined as original documents, data and records. They may include hospital records, clinical and/or office charts, laboratory data/information, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and x-rays.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, regulatory inspection(s), and will provide direct access to source data documents.

10.2 Case report forms

Data for individual subjects will be recorded on CRFs provided by the BPCA-CC. All entries must be complete. A case report form must be completed for each subject enrolled, including those removed from the study. If a subject is removed from the study, the reason for removal must be noted on the CRF by the investigator. The principal investigator must review and approve each CRF.

Case report forms must be current to reflect subject status at each phase during the course of the study. Subjects are not to be identified on the CRFs by name; appropriate coded identification and subject initials must be used. The investigator must keep a separate log of subject names and addresses. If requested as part of an FDA inspection, this log may be shown to the FDA investigator, but no copy should be provided so that confidentiality is protected.

Because of the potential for errors and inaccuracies in entering data onto CRFs, laboratory and other test results must be kept on file with the subject’s study dossier. Case report forms and copies of test results must be available at all times for inspection by the CRA for the site and the FDA.

11.0 Administration

11.1 Steering Committee

The Members of the Steering Committee will include the PODS PI and several of the site PIs (or Co PIs where applicable) at the subcontract sites, a representative(s) from the BPCA-CC, and the NICHD Project Officer. The NICHD Project Officer and the BPCA-CC staff will be non-voting members of the Steering Committee.

The Steering Committee will hold regular teleconferences. All Steering Committee members (or in special circumstances, their designee) will be required to participate in these meetings/teleconferences.

The Steering Committee will seek and accept advice from the NICHD, BPCA-CC and the DSMB, and will receive implementation recommendations from regular study coordinators' teleconference, to which it may delegate authority for minor implementation decisions. It will adopt a publication policy acceptable to all sites and will supervise the publication of results.

Should a problem at any given site arise, the PI (and Co-PIs) at that site will be contacted by one or more members of the Steering Committee to discuss the problem and to develop a plan for its resolution. A timeline and action-plan will be developed. This plan will be reported back to the Steering Committee. The timeline and outcome will then be monitored by the Steering Committee.

11.2 Responsibilities of the clinical investigator

Each of the site investigators will be responsible for the overall conduct of the study at their site. They must supervise all staff participating in each phase of the project, and be responsible for meeting the established timelines to the best of their ability. Finally, all PIs are ultimately responsible for the ethical conduct of the various studies at their sites and for timely completion of this study and communication of the results to the lead site.

12.0 Data Quality Control and Assurance

Prior to the initiation of the study, an investigator's meeting will be held with the BPCA-CC and MPODS network personnel, the investigators and their study coordinators for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF completion, simulation of study procedures and specimen collection methods, as applicable. In addition to the investigators' meeting, the study personnel at each site will be trained on the study procedures at a study initiation visit.

The CRAs will monitor each site throughout the study. At each visit, 100% source document review will be made against entries on the CRF and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and all applicable regulations.

After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary correction will be made to the database and documented via addenda or audit trail. A manual review of selected line listings will also be performed at the end of the study.

12.1 Site monitoring visits

Monitoring visits to the sites will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data collected on the CRFs. Participating sites and investigators will guarantee access to source documents and CRFs to the CRAs. The principal investigator and relevant site personnel will be available during the monitoring visits and will set aside sufficient time for the process.

12.2 Quality assurance and regulatory agency audits

The study sites may also be subject to quality assurance audits by the NICHD or its designees and appropriate regulatory agencies.

12.3 Data processing and data management

Clinical data processing and data management will be employed based on the procedures developed by the BPCA-CC in conjunction with the NICHD. All of the data entered into the

study data set (at the BPCA-CC) will be checked for valid values and ranges, between item logical consistency, and within-subject variation. Prior to any analyses, the distributions of the measures will be examined to aid in the selection of appropriate statistical techniques. Data transformations, utilizing nonparametric and semiparametric techniques, will be used in an attempt to normalize any data that is not normally distributed.

12.4 Ensuring confidentiality

A study number will be assigned for each subject. Data forms will be identified by subject number and initials. The database will not contain any personal identifiers other than subject number and initials.

12.5 Record retention

To enable evaluations and/or audits from Regulatory Authorities and NICHD or its designees, the investigators will keep records, including the identification of all medical charts and associated source documents and copies of all CRFs. The investigators will contact NICHD before disposing of any such materials.

13.0 Use of Information and Publication

13.1 Use of information

After the dataset for the study is finalized and main findings have gone into publication, the data from this project will be made available and shared through CD-ROM and/or a website. All project data will be stored without subject identifiers, so that the data that are shared cannot be linked back to any particular subject. The dataset will cover the outcome data on children collected over the course of the study.

13.2 Publication policy

Prior to a manuscript or abstract being submitted for possible publication or presentation, the Steering Committee, BPCA-CC, and NICHD must review the contents of the submission. More specifically, manuscripts, abstracts, and poster submissions must be submitted to the Steering Committee, BPCA-CC, and NICHD. Financial support from the NICHD will be acknowledged in all publications.

13.3 Data sharing plan

The dataset for this study will cover course and outcome data on children collected over the period of study. The data sharing plan will follow guidelines as dictated by institutional rules and approval of local IRBs of participating research sites, local, state and federal laws and regulations including the Privacy Rule. The final data sharing plan that will be employed by the BEST protocols will be developed in conjunction with the individual site PI's, the BPCA-CC, and the NICHD.

14.0 Completion of Study

The MPODS PI and MPODS investigators will complete this study in compliance with the protocol, and in a manner consistent with the timelines proposed. Continuation beyond published timelines must be mutually agreed upon by both the MPODS PI and the BPCA-CC.

The NICHD may terminate this study prematurely, either in its entirety or at a specific site, for reasonable cause. Written notice must be submitted within a reasonable amount of time prior to the intended termination date. An investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to the BPCA-CC and NICHD within a

reasonable amount of time prior to the intended termination date. Advance notice is not required by either party if the study is terminated due to safety concerns.

15.0 Investigator Agreement

I have received and reviewed the package insert for meropenem.

I have read the protocol and agree to conduct the study as outlined and in accordance with all applicable local, state, and federal regulation.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

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Appendix 1: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory

requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case, the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every subject entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.
5. In the treatment of a subject, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix 2: PK sampling times

Dose 1 PK-odd Group (infants with birthday on an odd date, e.g. 1st, 3rd, 5th, etc.)
1) Pre: anytime in the 24 hours prior to the first dose
2) Peak: 30 minutes to 1 hour after completion of first dose
3) 3-4 hours after completion of first dose
4) Trough: 7-8 hours after completion of first dose if Q8 hour dosing, or 10-12 hours after completion of first dose if Q12 hour dosing

Dose 1 PK-even Group (infants with birthday on an even date, e.g. 2nd, 4th, 6th etc.)
1) Pre: anytime in the 24 hours prior to the first dose
2) Peak: 1-2 hours after completion of first dose
3) 4-6 hours after completion of first dose
4) Trough: 7-8 hours after completion of first dose if Q8 hour dosing, or 10-12 hours after completion of first dose if Q12 hour dosing

Dose 5 PK-steady state (around 5th dose if possible, but may be done around the 4th, 6th, 7th, 8th, 9th or 10th dose)
1) Pre: anytime in the 3 hours prior to the 5th dose
2) Peak: 15 minutes-2.5 hours after completion of 5th dose
3) 4-12 hours after completion of fifth dose

Safety Steady-state Group
1. No Dose 1 PK samples should be drawn
2. Follow Dose 5 PK-steady state instructions above.

Appendix 3: Dosing Regimen

Low Dose

Infant	GA <32 weeks:	
	< 2 week PNA:	20 mg/kg q 12hr
	≥ 2 weeks PNA:	20 mg/kg q 8hr
Infant	GA ≥32 weeks:	
	< 2 week PNA:	20 mg/kg q 8hr
	≥ 2 weeks PNA:	30 mg/kg q 8hr

High Dose

Infant	GA <32 weeks:	
	< 2 week PNA:	20 mg/kg q 8hr
	≥ 2 weeks PNA:	30 mg/kg q 8hr
Infant	GA ≥32 weeks:	
	< 2 week PNA:	30mg/kg q 8hr
	≥ 2 weeks PNA:	40mg/kg q 8hr

Appendix 4: Study Definitions

Complicated intra-abdominal infections are defined as outlined in the WR. Complicated intra-abdominal infections are characterized by systemic inflammation and an intra-abdominal process extending into the peritoneal space that necessitates a surgical or percutaneous drainage procedure. The post-procedure findings of purulent exudates with inflamed or necrotic exudates with inflamed or necrotic tissue confirm the diagnosis. Examples of intra-abdominal processes in the youngest subjects that can result in peritonitis include:

- Necrotizing enterocolitis,
- Bowel obstruction with perforation,
- Hirschsprung's disease with perforation,
- Meconium ileus with perforation, and
- Spontaneous perforation

Suspected complicated intra-abdominal infections are defined as Necrotizing Enterocolitis (NEC) Stage 2 or greater by modified Bell's Criteria. This includes infants with portal venous gas or pneumatosis intestinalis by abdominal radiograph. These infants are eligible for study.

Empirical antibacterial therapy is defined as the antibacterial therapy that is administered at when cultures of normally sterile body fluid are negative, or results of normally sterile body fluid cultures are pending. Infants will receive empirical meropenem and aminoglycoside. The aminoglycoside is to be administered per local standard of care. The use of other antimicrobial agents is discouraged but may be added per local standard of care.

Empirical antibacterial therapy with meropenem per local standard of care: if an infant is given meropenem as empirical therapy, and such therapy is given in accordance with local standard of care, these infants are eligible for enrollment. In these cases, the infants do not require Stage 2 NEC, but the reasons for empirical therapy with meropenem should be documented in the CRF.

Antibacterial therapy for perforated bowel: If an infant has evidence of perforation or requires surgery, metronidazole should not be added given the anaerobic coverage of meropenem.

Definitive antibacterial therapy: If an infant has a positive culture from normally sterile body fluid (blood, CSF, peritoneal fluid, urine from in/out catheterization, etc.) then the infant may receive definitive therapy per local standard of care based on the sensitivity of the blood culture.

Definition of escalated empirical antibacterial therapy: if at any time the attending physician determines that a study participant's clinical condition has deteriorated while receiving initial empirical antibiotic therapy, the infant may receive additional empirical therapy as outlined in the escalation parameters below.

Escalation of antibacterial therapy will be considered a 'treatment failure'. These data will not be a primary endpoint for this trial, but will be used for planning subsequent trials. The following are guidelines that may be used to escalate therapy

Escalation for presumptive Gram negative rod (GNR) therapy: normally sterile body fluid yields Gram-negative bacilli and clinical deterioration. If the infant's condition has stabilized or

improves during empirical treatment, then empirical therapy should not be changed. The broad outline that constitutes a deterioration of clinical status is:

a. **Cardiopulmonary deterioration**: infants with refractory hypotension and evidence of tissue hypo-perfusion or who require escalation in the level of respiratory support after first dose of study medication. Refractory hypotension includes infants who require >20 mL/kg crystalloid or plasma and/or initiation of a vasopressor/inotrope medication. Evidence of tissue hypoperfusion includes oliguria and/or metabolic acidosis with a base deficit of 7 or greater on two blood gases not less than 4 hours apart. Escalation in respiratory support may include change from supplemental oxygen only to assisted ventilation with nasal CPAP or mechanical ventilation. For infants already receiving mechanical ventilation an increase in the mean airway pressure greater than 2 cm/H_20 constitutes escalation in respiratory support.

b. **Disseminated intravascular coagulation** (DIC): includes infants with thrombocytopenia (platelet count <100K) or elevation in prothrombin time >1.5 times the reference standard with elevation in fibrin degradation products.

NOTE—the clinician is not obligated to add additional therapy in the face of cardiopulmonary deterioration or DIC, but if the infant fits these broad guidelines, **may** add additional therapy and declare initial therapy failure.

Escalation of empirical GNR therapy: cultures are pending but infant has clinical deterioration as outlined above. NOTE—the clinician is not forced to add additional therapy, but the clinician **may** add additional therapy.

Escalation of definitive GNR therapy: if the infant has a GNR isolate that is not susceptible to either meropenem **or** an aminoglycoside, then appropriate therapy per local standard of care will be given. If the infant has any GNR isolated (by culture or Gram stain) from the CSF, then appropriate therapy per local standard of care will be given.

Escalation of presumptive Gram positive therapy: Gram positive therapy may be added if normally sterile body fluid yields Gram-positive cocci. NOTE—the clinician is not obligated to add Gram positive therapy, but **may** add Gram positive therapy. If the initial Gram-stain is subsequently identified as a resistant Gram-positive organism requiring therapy (e.g. MRSA, ampicillin resistant enterococcus, coagulase-negative staphylococcus) then the infant may be given definitive Gram positive therapy (see below). In these circumstances, the infant will **not** be considered a failure if one of the following occurs: the organism isolated requires definitive Gram positive therapy (see below), or once it is proven that the organism does not require Gram positive therapy (e.g. methicillin sensitive S. aureus), Gram positive therapy is discontinued.

Escalation of empirical Gram positive therapy is discouraged, but is permitted.

Escalation to definitive Gram positive therapy: if the infant has a positive culture from normally sterile body fluid (e.g. blood, cerebrospinal fluid, newly placed peritoneal drain, urine from in/out catheterization or suprapubic aspiration) that requires Gram positive therapy as outlined above, then the infant may receive Gram positive therapy to treat the infection in accordance with local standard of care. The infant is **not** considered a failure in this scenario

Empirical antifungal therapy: is defined as the administration of a systemic antifungal agent with cultures that are negative or pending**.** Empirical and definitive antifungal therapies are both allowed in this study.

Locally Diagnosed Clinical Seizures: behavioral phenomena thought to be seizure, and diagnosed as seizure by the local site Principal Investigator. Examples of these behavior include focal clonic (e.g., involving one limb, one side of the body, or the tongue and face), focal tonic, and generalized myoclonic seizures. Clinical attributes that support the diagnosis of seizure include slower and more rhythmic motor activity that cannot be stopped by restraint.

Locally Diagnosed EEG-confirmed Seizures: seizure activity confirmed by electrographic evidence by the local site Principal Investigator in consultation with a neurologist

Centrally Diagnosed Clinical Seizures: similar criteria as locally diagnosed clinical seizures, but also confirmed by the pediatric neurologist of the MPODS Clinical Events and Safety Committee.

Centrally Diagnosed EEG-confirmed Seizures: similar criteria to locally diagnosed EEG-confirmed seizures, but also confirmed by the pediatric neurologist of the MPODS Clinical Events and Safety Committee.

Non epileptic Seizure-Like Events (NELSE): clinical activity that may indicate the existence of neurologic dysfunction, but are not seizures. Clinical attributes that suggest NELSE are tremor, clonus, and motor automatisms that stop with restraint or are induced by touching or loud noises.

Appendix 5: Meropenem RFA Flow Diagram