Pediatric Trials Network

NICHD-2012-CLN01

Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥85th Percentile

Phase I Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Best Pharmaceuticals for Children Act (NICHD BPCA)

Funding Mechanism: Task Order

Protocol Number:	NICHD-2012-CLN01
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STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to, 45 CFR 46 (Human Subjects Protection, incorporating Subpart D: Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D: Additional Safeguards for Children in Clinical Investigations), and 21 CFR 56 (Institutional Review Board [IRB]).

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

SITE PRINCIPAL INVESTIGATOR STATEMENT

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

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

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

Redacted

Principal Investigator Name (Print)

Redacted

Principal Investigator Signature

7 OCTOBER 2013

Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

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

Redacted

Pediatric Trials Network Study

Principal Investigator Name (Print)

Redacted

Principal Investigator Signature

7 OCT 2013

Date

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Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BPCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cl	Clearance
Cl/F	Oral apparent clearance
CMP	Comprehensive Metabolic Profile
CRF	Case Report Form
CYP	Cytochrome
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mg	Milligram
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*

Abbreviations

N	Number (typically refers to subjects)
NIH	National Institutes of Health
PD	Pharmacodynamics
PG	Pharmacogenomic
PK	Pharmacokinetics
PO	Oral
SAE	Serious Adverse Event
t1/2	Half-life
TBW	Total Body Weight
Vd	Volume of Distribution
V/F	Oral apparent volume of distribution

Protocol Synopsis

Protocol Title:	Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLIN01
Phase:	I
Product:	Clindamycin phosphate (intravenous) Clindamycin hydrochloride (oral capsules) Clindamycin palmitate (oral solution)
Objectives:	Primary: Determine the pharmacokinetics (PK) of intravenous clindamycin in overweight and obese children and adolescents Secondary: 1) Determine the PK of oral clindamycin in overweight and obese children and adolescents 2) Characterize the safety profile of clindamycin in overweight and obese children and adolescents 3) Compare PK of clindamycin in obese children to non-obese children.
Study Design:	Prospective, multi-center, open-label, multiple-dose PK study of intravenous and oral clindamycin
Study Population:	Children ages 2 – < 18 years of age with body mass index (BMI) ≥ 85 percentile for age
Number of Subjects:	24–32 evaluable subjects
Number of Sites:	Up to 6 sites
Duration of Subject Participation:	Up to 18 days (1-day screening period, minimum of 2 doses prior to PK samples and maximum of 14-day treatment period, and 3-day observation period after study drug administration to monitor for serious adverse events)
Dose Schedule:	30–40 mg/kg/day dosed every 6 or every 8 hours with a maximum daily dose of 2.7 grams/day
Estimated Start:	October 2012
Estimated Time to Complete Enrollment:	Approximately 24 months

Protocol Synopsis

Inclusion Criteria:	1) 2 years – < 18 years of age at the time of first dose of study drug 2) Suspected or confirmed infection OR receiving intravenous clindamycin per routine care 3) Negative urine pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug 4) BMI ≥ 85th percentile for age and sex, based on CDC recommendations 5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)
Exclusion Criteria:	1) The following apply only to those who are NOT already receiving clindamycin as part of routine care: a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin b. History of *C. difficile* colitis with previous administration of clindamycin c. Aspartate aminotransferase (AST) > 120 units/L d. Alanine aminotransferase (ALT) > 210 units/L e. Total bilirubin > 3 mg/dL f. Serum creatinine > 2 mg/dL g. Receiving a neuromuscular blocker as part of therapy (see **Appendix II**) 2) Previous participation in the study 3) Subject is on prohibited medication or herbal product (see **Appendix II**) 4) Subject is receiving extracorporeal life support (ECLS) 5) Subject is post-cardiac bypass (within 24 hours) 6) Subject on inotropes/pressors 7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

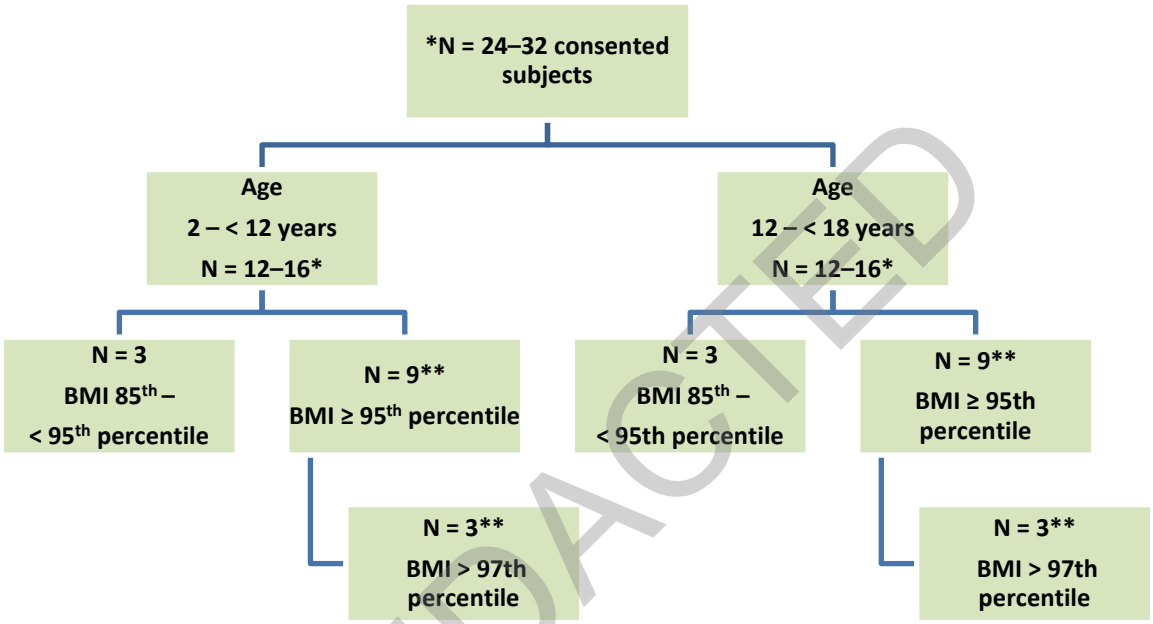
Protocol Synopsis

Table 1. Study Event Table

Study Event/Day	Screening/ Study Day 0	Study Day 1 (any dose after the 1st dose of IV clindamycin; oral PK with 4th dose or later)	Study Day 2–14	End of Therapy OR early Withdrawal or Discontinuation	3-Day Post-treatment Phone Follow-up
Informed consent/ assent & HIPAA	X				
Medical history	X				
Demographics	X				
Concomitant medications	X	X	X	X	X
Infection history	X	X			
Physical examination	X			X	
Weight	X				
Height	X				
BMI	X				
Laboratory evaluation[a]	X			X	
α-1 glycoprotein (ELISA kit)[b]	X				
Laboratory evaluation (6.6.1 Table 2—if obtained as part of routine care)		X	X		X
Urine pregnancy test (female only)	X				
Feeding status (during PO PK portion only)		X			
Discarded scavenged samples[c]		X	X		
Clindamycin IV or PO[d]	X	X	X[f]		
PK samples[e]		X			
AE/SAE	X	X	X	X	X

[a]CBC, CMP.
[b]May be performed at any time during the study if not obtained at baseline.
[c]Discarded blood cells may be collected at any time during the study.
[d]Group assignment (see Figure 1).
[e]PK sampling (Table 3, see Section 6.6.2).
[f]IV clindamycin will be continued per treating physician; when switched to PO, subject will participate in PO PK study.

Figure 1. Schematic/Description of Study Design



*IV subjects who transition to oral clindamycin will participate in the oral PK study.
**Minimum of 3 subjects with BMI > 97th percentile in each age group.

1 KEY ROLES

For questions regarding this protocol, contact:

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Over the past decade, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a leading cause of hospitalization for children and adolescents in the United States (1). Consequently, the use of antimicrobial agents active against MRSA has become more prevalent (2). Specifically, the use of clindamycin among children hospitalized with *Staphylococcus aureus* infections increased from 21% in 1999 to 63% in 2008. At the same time, rates of childhood obesity have continued to remain high. Recent national data demonstrate that 17% of children aged 2–19 years in the United States are obese (body mass index [BMI] ≥ 95th percentile) and 12.3% are morbidly obese (BMI ≥ 97th percentile) (3). Obese patients have a greater likelihood of complications from infectious diseases and are at increased risk of developing *Staphylococcus aureus* infections. Therefore, an understanding of the PK of clindamycin in this population is critical to ensure appropriate interventional therapy.

Clindamycin, a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin (4), is approved by the U.S. Food and Drug Administration for the treatment of pediatric and adult patients with respiratory tract, female pelvis and genital tract, and skin and soft tissue infections with susceptible bacteria including streptococci, pneumococci, and staphylococci. Clindamycin is also approved in adults for septicemia and intra-abdominal and serious infections with susceptible anaerobic bacteria (package insert).

Clindamycin is approximately 90% protein-bound. It is metabolized by the liver and excreted via the liver, bile, and kidneys. Impaired renal function modestly decreases the elimination of clindamycin; however, dosage adjustment is not required with renal dysfunction (4). Clindamycin phosphate (intravenous [IV] formulation) is rapidly converted to active clindamycin and has an elimination half-life of about 3 hours in adults and 2.5 hours in children (package insert). The drug penetrates well into all tissues, with the exception of the brain and cerebral spinal fluid. It is actively taken up and concentrated within the phagocytic cells. Clindamycin binds to the 50S subunit on the bacterial ribosome and inhibits protein synthesis by interfering with the formation of initiation complexes, thus inhibiting exotoxin production (4). Clindamycin exhibits time-dependent killing; and efficacy is correlated with the time clindamycin concentrations exceed the minimum inhibitory concentration of the pathogen of interest. A summary of clindamycin serum concentrations in non-obese children is found in Appendix IV.

Variability in serum and tissue concentrations has been reported in obese patients (4). The underlying premise is that this is due to physiologic changes that alter a drug's volume of distribution (Vd) and body clearance (Cl) (5,6). Thus, obese patients may be dosed inappropriately if fixed or "adult" doses are used (under-dosed) or if weight-based dosing is used (over-dosed) (5,6). Because critically ill obese patients with infections are reported to have a worse outcome than non-obese patients (7), it is imperative to determine if the disposition of and response to clindamycin may be altered compared to healthy children with an infection. In addition, sub-therapeutic drug concentrations may increase the development of resistant

organisms. Thus, it is important to perform pharmacokinetic (PK) and pharmacodynamic (PD) studies in the obese pediatric population to ensure that these patients are being optimally dosed with medications designed to treat infections. There are no currently available PK (or PD) data to guide clindamycin dosing in obese pediatric or adult patients. This proposal will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years.

2.2 Scientific Rationale

Selection of the correct drug dose and dose regimen is the most important decision in ensuring optimal pharmacotherapy. Defining an optimal regimen requires a clear understanding of the drug's PK, PD, and, for many compounds, pharmacogenomic (PG) profiles. Understanding these characteristics for drugs used in pediatrics is imperative to determine optimal dose regimens across the pediatric age continuum.

Clinically, drug dosing in pediatrics is individualized to age by basing the drug dose on a patient's body weight and the dose interval on the functional capacity of the drug's clearance pathways. This approach assumes, though inaccurately, that a drug's Vd and body Cl are directly proportional to a patient's body weight. Despite this lack of proportionality, the majority of pediatric patients favorably respond to weight-based drug dosing. However, as the potency of newer drugs increases and the need for more precise drug dose regimens expands, better-defined dose regimens based on careful assessment of the drugs' integrated PK-PD-PG profiles across the pediatric age continuum are needed (8). Complicating this paradigm are the substantially increasing numbers of children and adolescents who are obese, and even morbidly obese, and the lack of data on disposition in the obese population. Clinical trials of new drugs focused on FDA labeling exclude obese patients, leaving the determination of dosing regimens in the obese for post-marketing, often investigator-initiated studies.

Antibiotic Dosing Regimens Based on PK-PD Modeling
Prior to our understanding of the integrated PK-PD characteristics for antibiotic drugs, antibiotic dosing regimens were mostly based on perceived maximum tolerated doses often related in some manner to the target pathogen minimum inhibitory concentration (MIC). Integration of an antibiotic's PK with PD allows for the determination of the optimal dose regimen across the spectrum of antibiotic drugs (9,10). In addition, this more quantitative approach permits comparisons of different antibiotic drugs for a specific infection and far more accurate predictability of patient response. The specific antibiotic PK-PD characteristic used to predict outcome (i.e., bacteriologic eradication) appears to be mostly dependent on whether the drug's bacterial killing is concentration- or time-dependent. Clindamycin is most often described as a "time-dependent antibiotic with moderate persistent effects," and as such, the best predictor of bacterial killing appears to be the ratio of the area under the clindamycin (free, unbound) drug concentration time curve (AUC) divided by the targeted pathogen MIC (i.e., fAUC/MIC) (10). To accurately determine this pivotal PK-PD parameter, what is needed is a comprehensive understanding of the drug's PK profile across the age spectrum while incorporating the spectrum of pathophysiologic changes and differing body habitus. For clindamycin, these data are not available.

Clindamycin Pharmacokinetics
Limited published clindamycin PK data exist and encompass < 100 neonates, infants, and children. In neonates, clindamycin elimination is delayed compared with older infants and

children—mean elimination half-life (t ½) values of 8.7 vs. 3.6 hours, respectively (11,12). Regardless of age group studied, variability was observed in clindamycin t ½, Vd, AND systemic Cl. In addition, some studies report variable serum clindamycin concentrations (bioactivity) following parenteral dosing (11,13). Despite this variation in drug disposition, which is observed in both children and adults, bioactive serum clindamycin concentrations remain therapeutic following routine parenteral (intramuscular [IM], IV) or oral dosing. Considering that clindamycin, an antibiotic, is used to treat infections caused by susceptible pathogens responsible for infectious diseases regardless of patient age, pediatric clindamycin development strategies need only focus on the drug's safety and PK profile to ensure similar systemic exposure. Available clindamycin PK data support close similarity for clindamycin systemic exposure (i.e., bioactive serum clindamycin concentrations and AUC) in older infants, children, and adults following comparable mg/kg doses (11,13–18). As noted above, clindamycin PK in premature and full-term infants is, as expected, different than that observed in older patients (11,12). This foundation of data underscores the importance of studying clindamycin disposition in the obese pediatric patient.

Clindamycin is extensively bound to plasma protein, primarily to alpha 1 acid glycoprotein, and, with the exception of the brain or cerebrospinal fluid, effectively penetrates body tissues and fluids. The drug is metabolized primarily by the cytochrome (CYP) P450 isoenzyme CYP3A4 to two primary, antimicrobial active metabolites, a sulfoxide and to a lesser extent N-demethylclindamycin (19). Although only limited data are available for current clindamycin pediatric dosing regimens, the regimens employed clinically have been used for decades with apparent success. Nevertheless, clindamycin optimal dosing regimens in pediatrics remain unknown. Furthermore, the influence of obesity on clindamycin disposition is unknown and may have a far greater negative impact on patient outcome due to ill-defined, clinically extrapolated dosing.

Drug Dosing and Obesity

Data defining optimal drug dosing in the obese and morbidly obese adult patient are very limited and virtually non-existent in pediatrics. Drug dosing on total body weight (TBW) in the obese patient has the real risk of overdosing the patient, resulting in an increased incidence of adverse effects, while dosing on ideal body weight (IBW) can lead to serious under-dosing. In obese adults, IBW is increased by 20–40%, which is unaccounted for when using the many mathematical formulas available to calculate dosing based on a person's IBW. This deficiency may partially explain the inaccuracy of drug dose regimens for obese patients based on IBW formula estimations (20–25).

The influence varying degrees of obesity have on important physiologic functions across the age continuum in pediatrics is unknown. In adults, sparse data suggest that obese adults may have altered tissue blood flow rates due to inherent differences in blood flow to lean (greatest amount) and adipose tissue, impaired cardiac function, and alterations in phase I and II metabolism. Although intuitive, one might assume that a drug's Vd would be increased in obese patients for lipophilic compounds, though in fact, for the few drugs assessed, the Vd is highly variable. Similarly, Cl is also highly variable in the obese population, underscoring the need to determine drug disposition characteristics not only across the age continuum but also with increasing degrees of obesity (20–23). No such data are available for the pediatric patient, but these data combined underscore the need to critically assess a drug's disposition relative to age and body habitus. Furthermore, for antibiotics whose efficacy is dependent on achieving

effective concentrations at the infectious site, interfaced with the organism, optimal dosing in the obese pediatric patient must be defined (5,6).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of Blood Draws
There are small risks to blood sampling, usually some pain/discomfort with the blood stick. Every effort will be made to avoid additional (to standard of care) sticks for this study by timing clinical blood draws to coincide with timed samples when possible and the use of existing IV lines when feasible for the blood draws.

Risks of Clindamycin
From the FDA label and review of the literature, the following are adverse reactions of clindamycin: antibiotic-associated colitis, pseudomembranous colitis, abdominal pain, nausea, and vomiting; hypersensitivity reactions (maculopapular rash and urticaria have been observed during drug therapy; generalized mild-to-moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions; rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin; a few cases of anaphylactoid reactions have been reported). Organ systems that are affected include skin and mucous membranes (pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported); liver (jaundice and abnormalities in liver function tests have been observed during clindamycin therapy); renal system (although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances); hematopoietic (transient neutropenia [leukopenia] and eosinophilia have been reported; reports of agranulocytosis and thrombocytopenia have been made; no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances); local reactions (pain, induration, and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion); musculoskeletal (rare instances of polyarthritis have been reported); cardiovascular (rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV administration). There is minimal additional risk to the subjects who are receiving clindamycin as part of their routine medical care.

2.3.2 Known Potential Benefits

The subject may benefit from the use of the study drug; however, participation in this study has no other potential benefits to the subjects. The results of this study may benefit overweight and obese subjects in the future who require clindamycin therapy.

3 OBJECTIVES

Primary Aim
Characterize the PK of multiple-dose IV clindamycin in overweight and obese children and adolescents.

Secondary Aims
1. Characterize the PK of multiple-dose oral clindamycin in overweight and obese children and adolescents.
2. Characterize the safety profile of clindamycin in overweight and obese children and adolescents.
3. Compare PK of clindamycin in obese children to non-obese children

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1. PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUCtau)

3.1.2 Secondary Outcome Measures

1. PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2. Safety profile: Adverse events will be collected during and after study drug administration..

4 STUDY DESIGN

This will be a prospective, open-label PK and safety profile study of multiple doses of IV and oral clindamycin in overweight and obese children 2 – < 18 years of age. The total study duration is expected to be approximately 24 months; each subject will participate in the study for up to 18 days (screening day; treatment days 1–14 [may be as short as 2 days] followed by an observation period of 3 days post discontinuation of clindamycin therapy or after day 17 (on day 18) of therapy in those who are treated with more than 14 days of clindamycin).

5 Study Population

Selection of the Study Population

Eligible subjects ages 2 – < 18 years will be identified through the inpatient units at each participating site. There will be up to 32 evaluable subjects (defined in Section 10.3) enrolled; however, target enrollment will be 24 subjects. If dosing changes are suggested by the interim PK analysis (see **Section 10.3**), approximately 8 additional subjects will be enrolled. Twelve to 16 subjects will be enrolled in each of the following age groups: 2 – < 12 years and 12 – < 18 years of age. Subjects will be further stratified into 1 of 2 groups based on their BMI (85^{th} – < 95th percentile, and ≥ 95th percentile). No more than 3 subjects with BMI in the 85^{th} – < 95th percentile will be enrolled in each age group. Participating sites will collectively enroll a minimum of 3 subjects with BMI > 97^{th} percentile in each age group.

5.1 Inclusion/Exclusion Criteria

The investigator or other study site personnel will document in the source documents (e.g., the hospital chart) that informed consent and assent (if applicable) were obtained. Laboratory tests or non-pharmacologic treatment procedures that were performed and considered "routine care" within 72 hours of first dose of study drug may be used for screening procedures required by the protocol and recorded in the case report form (CRF).

Inclusion Criteria

1) 2 years – < 18 years of age at the time of first dose of study drug
2) Suspected or confirmed infection OR receiving IV clindamycin per routine care
3) Negative urine pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug
4) BMI ≥ 85^{th} percentile for age and sex, based on CDC recommendations
5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

Exclusion Criteria

1) The following apply only to those who are NOT already receiving clindamycin per routine care:
   a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin
   b. History of *C. difficile* colitis with previous administration of clindamycin
   c. AST > 120 units/L
   d. ALT > 210 units/L
   e. Total bilirubin > 3 mg/dL
   f. Serum creatinine > 2 mg/dL
   g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II**)
2) Previous participation in the study
3) Subject is on prohibited medication or herbal product (see **Appendix II**)
4) Subject is receiving extracorporeal life support (ECLS)

5) Subject is post-cardiac bypass (within 24 hours)
6) Subject on inotropes/pressors
7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

5.2 Treatment Assignment Procedures

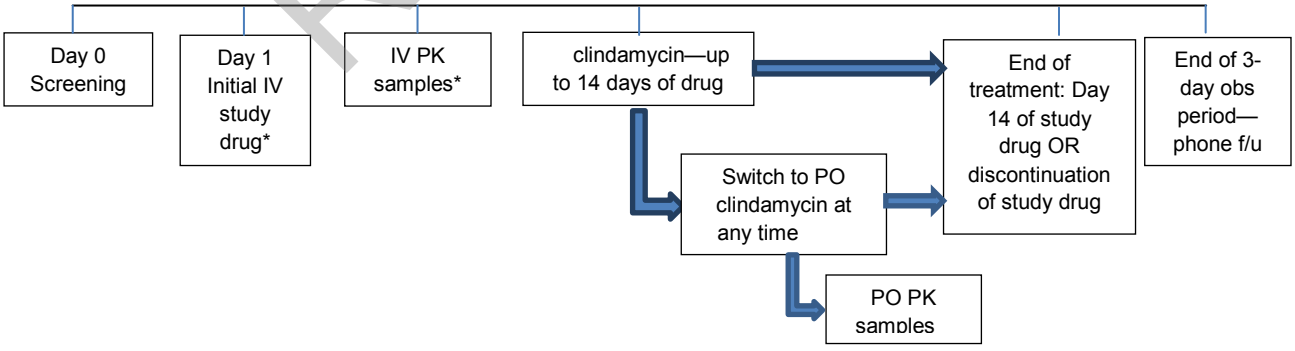
This will be an open-label PK study. Subjects will be assigned to age groups based on age upon first dose of study drug and to a BMI group based on BMI at study entry.

5.2.1 Duration of Study Participation

Duration of therapy will be up to 14 days.) for children who receive the first dose of clindamycin as the study drug. All subjects will begin on IV therapy and must receive at least 2 doses of IV clindamycin to participate in the study. The total duration of therapy with clindamycin will be determined by the treating physician for those children who are receiving clindamycin as part of routine care; however, only 14 days of therapy from the time of enrollment will be considered as study drug. If therapy extends beyond 14 days, the study follow-up visit/call will occur on day 18 (after completion of 3 safety observational days [72–96 hours]). Patients who are on other antimicrobial agents may enroll in this study and receive up to 3 doses of IV clindamycin and 4 doses of oral clindamycin. Subjects who transition to oral clindamycin may return as outpatients to complete the PK portion of the study.

Total duration of study participation will be up to 18 days. This will comprise a 1-day screening period; a minimum 2 doses of IV and 4 doses of oral clindamycin before PK sampling begins for IV and oral routes, respectively; a maximum 14-day treatment period; and a 3-day post-study observation period to monitor for serious adverse events. The 3-day post-treatment visit may be a phone follow-up.

Figure 2.Timeline



*Minimum of 2 doses of IV clindamycin before IV PK period.
**Minimum of 4 doses of PO clindamycin before PO PK period.

5.2.2 Replacement Subjects

Subjects in the IV portion of this study who are unable to provide at least 3 timed PK samples may be replaced.

5.2.3 Reasons for Subject Withdrawal

A subject or his/her parent/guardian may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time. Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject or investigator noncompliance with the study protocol
- At the request of the subject, investigator, treating physician, or sponsor
- Adverse reaction or suspected adverse reaction.

Subjects are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. The subject who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations, and will be provided appropriate care under medical supervision until the symptoms of any adverse event (AE) resolve or the subject's condition becomes stable. Subjects withdrawn from the study due to an AE must be followed per protocol (see **Section 8.2.4**).

5.2.4 Termination of Study

This study may be terminated at any time by NICHD, the Investigational New Drug Application (IND) sponsor, or the Data Monitoring Committee (DMC) if serious adverse reactions occur in 2 or more subjects that are directly related to study drug, or if, in NICHD's judgment, there are no further benefits to be achieved from the study. A study site may be terminated if the investigator does not adhere to the study protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

See the schedule of study events and procedures on page xi (**Table 1**).

1. Medical history will be obtained by interview with the parent/legal guardian/subject and from the subject's medical records.
2. Concomitant medications of interest administered within 72 hours prior to and during the period of administration of study drug, including herbal products of interest, will be recorded (see **Appendix II**).
3. Physical examination, including abnormal physical findings, height (measured standing if possible), and weight, will be obtained. BMI will be calculated from height and weight using the following formula: BMI = [weight (kg) / (stature (cm))^2] x 10,000. Please refer to the website for the Centers for Disease Control (CDC) pediatric BMI calculator (http://apps.nccd.cdc.gov/dnpabmi/). The BMI percentile will be obtained using the BMI calculator and verified using the age- and sex-specific CDC BMI charts (**Appendix I**).
4. The safety laboratory testing complete metabolic panel (CMP) and complete blood count (CBC) will be performed at each site's local laboratory. Baseline CMP and CBC may be used if obtained as part of routine care within 72 hours prior to study enrollment. The urine pregnancy test will also be performed at the local laboratory (within 24 hours prior to study enrollment). Alpha-1-glycoprotein will be measured using an ELISA kit (central laboratory) at one time point after consent.
5. PK samples will be obtained with the second or subsequent doses of clindamycin for IV PK samples and after 4 doses of oral clindamycin (see **Section 6.6.2**).

6.2 Screening

Research staff at sites will screen potential subjects for eligibility requirements. A partial waiver will be completed with the IRB submission at each site to allow for screening of potential subjects prior to obtaining informed consent.

6.3 Enrollment/Baseline

Baseline/Pre-Dose Assessment (Day 0)
After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA documents, the subject has signed assent (if applicable), and after it has been determined that the subject satisfies all inclusion and no exclusion criteria, the following evaluations will be performed and recorded in the CRF:

1. Subject demographics
2. Physical examination, including weight, height, and BMI
3. Pertinent medical history
4. Concomitant medications (72 hours prior to first dose of study drug)

5. Laboratory determinations (see **Table 2, Section 6.6.1**)
6. Culture results of blood, urine, sputum, or wound (if obtained as part of routine care) within 72 hours prior to the first dose of study drug
7. For subjects receiving clindamycin per routine care, the date and time for the doses administered prior to first dose of study drug will be recorded (up to a maximum of 6 prior doses)
8. Urine pregnancy test (females only who have reached menarche) within 24 hours of study enrollment

Assessments/Procedures (Days 1–14)
The subject will start study drug upon completion of the pre-assessment, or, if s/he was already receiving clindamycin (at the study-recommended dose), s/he will continue receiving that dose of clindamycin. If s/he was receiving clindamycin at a dose lower than the study-recommended dose, the dose will be changed to be in compliance with the protocol. Total body weight will be used to calculate the absolute dose administered. Refer to **Section 7.1.2** for dosing. Subjects who transition to oral therapy will participate in the oral-dose PK portion.

The following assessments will be conducted after the subject receives the first dose of clindamycin after study enrollment and throughout therapy up to day 14:

1. Concomitant medications of interest (see **Appendix II**)
2. Start date/time and stop date/time of clindamycin administration and flush date/stop time after IV administration
3. Feeding status (during PO PK portion only): NPO, clear liquids, full feeds, etc.
4. Collection of PK samples (including date/time); see **Section 6.6.2**
5. Laboratory results for laboratory tests of interests (see **Section 6.6.1**)
6. Collection of culture results (if available)
7. Adverse events (see **Section 8.2.1**)

6.4 End of Therapy OR Early Withdrawal/Discontinuation

The following assessments will be conducted at early withdrawal or end of therapy:

Concomitant medications of interest (see Appendix II**)**

1. Physical examination
2. Laboratory evaluations (see **Section 6.6.1**)
3. Adverse events (see **Section 8.2.1**)

6.5 Follow-up Safety Phone Call

Assessments/Procedures (Day 3 Post Treatment): This visit will be a phone follow-up unless the subject is still hospitalized. This assessment must occur at least 72 hours but no more than 96 hours after the last dose of study drug. The following information will be obtained:

1. Adverse events (see **Section 8.2.1**)
2. Concomitant medications
3. Any labs collected

6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

The safety laboratory testing (CMP and CBC) will be performed in the local laboratory at each site. CMP and CBC performed as part of routine care within 72 hours prior to enrollment may be used for baseline laboratory tests. A CBC and CMP will be obtained at the end of therapy (any hematology or chemistry values obtained within ± 24 hours of discontinuation of study drug or within ± 24 hours of completion of 14 days of study drug (if they are continuing clindamycin beyond 14 days) may be used as end-of-treatment laboratory values). If these laboratory tests have not been performed as part of routine care, they will be performed for the study per the protocol schedule. The urine pregnancy test will also be performed at the local laboratory. Alpha (α)-1-glycoprotein will be performed once during the study using an ELISA kit (central laboratory).

Table 2. Laboratory Evaluations

Hematology	Serum Biochemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Platelets	Chloride
White blood cells	Bicarbonate
	Total calcium
	Glucose
	Creatinine
	Blood urea nitrogen
	Total protein
	Albumin
	Aspartate aminotransferase
	Alanine aminotransferase
	Bilirubin
	α-1 glycoprotein (central laboratory)

6.6.2 Special Assays or Procedures

PK Samples
Blood (0.5 mL) will be collected with scheduled IV and oral doses of clindamycin for clindamycin plasma concentration determinations (see **Table 3** below for schedule). In subjects receiving IV clindamycin, PK samples should be collected from a site separate from the site of administration. PK samples in subjects on IV clindamycin will be collected with any dose after the first dose of study drug (excluding the first dose), and, for PO clindamycin, PK samples will be collected with the fourth dose or any dose after the fourth dose. The PK sampling will be drawn according to the following schedule relative to the end of infusion (IV PK) or actual time of oral administration (PO PK).

Table 3. PK Schedule

Scheduled PK Sampling Times				
Time (hours)*	**IV dose***		**PO dose**	
	Q6h	**Q8h**	**Q6h**	**Q8h**
Pre-dose 0 (within 15 minutes prior to the dose)	**X****	**X****	**X****	**X****
0.5 (± 5 minutes)	**X****	**X****	N/A	N/A
1–1.5	X	X	**X****	X**
3–4	**X****	**X****	**X****	--
5–6	--	X	--	**X****
Pre-dose (will depend if on q6h or q8h dose schedule)	**X****	**X****	**X****	**X****
Total number of samples	5	6	4	4

* Time starts at end of flush after the 30-minute infusion.
** Priority samples (see paragraph below).

Every effort should be made to collect all PK samples for each subject. Collection of PK samples should be timed with collection of laboratory tests per standard of care to minimize blood draws specifically for the study. If it is impractical to collect all PK samples during the same dosing interval, samples can be obtained at different dosing intervals. If it is impossible to obtain all PK samples for each subject, **PK samples can be prioritized to include:**

a) **For IV administration: pre-dose, 0.5 hours, 3–4 hours, and pre-next dose**
b) **For oral administration: pre-dose, 1–1.5 hours, 3–4 hours (q6h dosing), 5–6 hours (q8h dosing), and pre-next dose**

Clindamycin concentrations in plasma will be measured at a central laboratory using a validated bioanalytical assay. In addition, scavenged samples will be obtained.

Scavenged Plasma Sampling
Plasma samples collected in EDTA tubes during the course of therapy (~100 µL plasma or ~200 µL whole blood) will be procured, after consent. A maximum of 10 scavenged plasma samples will be collected per subject. Collection may begin with any specimen collected after the first dose of study drug through 24 hours after the last dose of study drug. The date and time of sample collection, as well as the date and time the sample is frozen, will be collected for all scavenged samples.

Minimizing Blood Loss
To minimize the amount of blood sampling, hematology and chemistry laboratory measures will be obtained only at baseline and end of study. If they have been obtained as part of routine care within 3 days prior to enrollment into the study, the baseline CMP and CBC do not need to be repeated. The PK sampling scheme will be employed such that no more than a total of 8 mL (< 3 mL/kg) of blood is obtained from each subject for PK analysis. Plasma samples will be collected in 0.5 mL blood aliquots.

6.6.3 Specimen Preparation, Handling, Storage, and Shipping

Detailed information for collection, labeling, preparation, handling, storage, and shipping of specimens is detailed in the manual of procedures (MOP).

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

A dose of 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 g/day is selected based on current labeling. Patients who are receiving clindamycin as part of their routine care are also eligible to participate if their dose can be adjusted to be within the study dosing guidelines upon enrollment. The dose administered will be based on TBW. Because bioavailability is estimated at 85%, the same dose will be used for oral administration as is used for IV dosing. Both solution and capsule preparations will be included in this study because both oral formulations are utilized in clinical practice, and it will allow the inclusion of those patients who cannot swallow pills. In the absence of PK data, we assume that drug clearance will be comparable in obese pediatric patients compared to non-obese pediatric patients. Therefore, a dosing regimen 30–40 mg/kg per day and a maximum dose of 2.7 g/day should provide exposures similar to those used in children and adolescents with a normal BMI. It is predicted to be safe in the obese population because similar doses are currently used per routine care.

7.1.2 Dose and Timing

Both q6h and q8h dosing will be allowed for both oral and IV dosing of clindamycin. For children receiving clindamycin as part of clinical care, this protocol will not prescribe a route of administration or dosing interval; the dose, route of administration, and dosing interval prescribed by the treating physician will be recorded on the CRF. However, if the prescribed dose is less than the lowest dose for this study, the dose of clindamycin will be changed to comply with the study-recommended dose. See **Section 5.2.1** for duration of therapy.

IV dosing: A minimum of 2 doses of IV clindamycin will be administered. The dose administered will be based on TBW at 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 grams/day. The drug will be administered over 30 minutes. The venous access line will be flushed per local practice of the completion of IV administration, and the time of the end of flush will be documented.

Oral dosing: For those subjects who are receiving clindamycin as a solution, they will receive 30–40 mg/kg/day divided q6h or q8h. For those subjects receiving the capsule formulation, they will receive the dose of clindamycin defined in **Appendix III**. Only whole capsules will be used. The oral solution will be used for those subjects who cannot swallow capsules. During the PO phase of the study, PK samples should be obtained with the fourth dose of PO clindamycin (but may be collected with a later dose if unable to do the fourth dose). No more than 12 PO study drug doses will be administered as part of this study.

7.1.3 Formulation, Packaging, and Labeling

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules.

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles for reconstitution.

Each formulation is approved for use in the United States.

7.1.4 Product Storage and Stability

Clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules), and clindamycin palmitate (PO oral solution) will all be stored at room temperature (20–25^0 C). Diluted clindamycin phosphate (IV) is stable at room temperature for at least 16 days and refrigerated for at least 32 days. Reconstituted clindamycin palmitate hydrochloride, USP for oral solution is stable for 2 weeks at room temperature and should not be refrigerated. See the MOP for detailed information.

7.2 Preparation and Administration of Study Intervention/Study Drug

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL. The drug will be infused over 30 minutes. Infusion rates should not exceed 30 mg/minute. The pharmacy will prepare the IV formulation, and the dose administered will be based on TBW.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules, and the dose will be dispensed based on TBW (see **Appendix III** for dosing).

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles and will be prepared in the pharmacy at each site based on the reconstitution recommendation in the label. The dose administered will be based on TBW.

Refer to the MOP for additional details regarding drug procurement, drug preparation, and administration.

7.3 Modification of Study Intervention/Investigational Product for a Subject

No dosing adjustments are required for hepatic or renal impairment.

7.4 Accountability Procedures for the Study Intervention/Study Drugs

Each site will provide drug for their study subjects. The study product accountability records will be maintained in the pharmacy study binder for clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules) and clindamycin palmitate (PO oral solution). See MOP for specific details related to investigational product accountability.

7.5 Assessment of Subject Compliance w/ Study Intervention

Compliance with dosing will be determined using the pharmacy accountability logs and the subject's medication administration record. For those subjects who are discharged on oral clindamycin and have not completed the PO PK visit, the subject will keep a drug administration diary and all drugs will be accounted for at the outpatient PK study visit.

7.6 Concomitant Medications/Treatments

Prohibited drugs are listed in **Appendix II**.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

AEs will be collected during and after study drug administration and for 3 days following end of therapy with clindamycin. Results will be tabulated by MedDRA System Organ Class and Preferred Term.

8.2 Methods & Timing for Assessing, Recording, & Analyzing Safety Parameters

AEs will be collected from the time of consent, throughout the period of study drug administration, and for 3 days following end of therapy with clindamycin. See **Section 8.6** for clarification for AEs identified at the 3-day follow-up visit and for serious AEs (SAEs). Safety will be assessed by frequency and incidence of AEs and SAEs. The Best Pharmaceuticals for Children Act (BPCA) safety monitoring committee (DMC) convened by NICHD will review data and safety information from study subjects.

8.2.1 Adverse Event

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

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

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

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

1. Death
2. Life-threatening AE (“life-threatening” means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.2.2 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, investigational plan, or informed consent.

8.2.3 Identification of Events and Timeframe for Reporting

As all subjects in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after consent has been obtained. The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome. Any event beginning more than 3 days after the last dose of study drug will not be captured.

8.2.4 Follow-up of Adverse Events

AEs ongoing at the time of the last dose of study drug will be followed up to 3 days after the last dose of study drug. AEs that resolve during the study or follow-up period will have the resolution date documented in the CRF. Adverse events that are identified at the last assessment visit/phone contact (or at the early termination visit) must be recorded on the AE CRF, with the status of the AE noted. Any events that are identified at the last assessment visit/phone contact will be followed for an additional 3 days for AEs and 10 days for SAEs and if still ongoing can be "resolved by convention". All serious suspected adverse reactions will be followed until resolution. All enrolled subjects in both cohorts who receive at least 1 dose of clindamycin will be followed for safety.

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Subject is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. **MODERATE**: Subject experiences enough symptoms or findings to require intervention
3. **SEVERE**: Subject experiences symptoms or findings that require significant intervention

8.4 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction. ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.5 Reporting Procedures and Timeframe for Reporting

All AEs will be entered into the data system within 72 business hours of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties encountered when entering the event into the electronic data capture (EDC) system, the SAE will be reported to the data coordinating center (DCC) by telephone or FAX communication. Investigators must submit safety reports as required by their local IRB, independent of the reporting requirements specified in the protocol.

8.5.1 Serious Adverse Events

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC, IND sponsor, and funding sponsor (NICHD). The BPCA DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.5.2 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The sponsor or his representative will submit expedited safety reports (IND safety reports) to the FDA and other regulatory agencies as necessary, and will inform the DMC and investigators of such regulatory reports. Site investigators must submit IND safety reports as required by their IRB. Documentation of the submission to and receipt by the IRB should be retained for each IND safety report. The sponsor will submit a progress report of the investigation annually, which will include a summary showing the most frequent and most serious adverse events by body system.

8.6 Type and Duration of Follow-up of Subjects after Adverse Events

Adverse events will be followed by the investigator or a clinician member of the study team in person if the subject is hospitalized for an AE or SAE. If the subject is not hospitalized, the investigator or a clinician may review the subject’s medical record, contact the subject by phone, or contact the subject’s primary care physician for follow-up.
Subjects withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator. Refer to Section 8.2.4 for follow-up of AEs/SAEs. The medical monitor or study principal investigator must be notified if the AE may relate to overdose of study treatment.

8.7 Halting Rules

Subject safety data will be reviewed on an ongoing basis to monitor for halting criteria.

The study enrollment and dosing will be halted for a safety review by the BPCA DMC if serious adverse reactions occur in ≥ 2 subjects.

Furthermore, the NICHD, the IND sponsor, the DMC, and the investigators shall have the right to recommend termination of this study at their discretion. Possible reasons for termination of the study include, but are not limited to:

1. Adverse events
2. Unsatisfactory enrollment with respect to quantity or quality

The study may be placed on hold or terminated at a site(s) for the following reasons:

1. Inaccurate or incomplete data collection
2. Falsification of records
3. Failure to adhere to the protocol

8.8 Safety Oversight (Safety Monitor plus DMC)

This study will be overseen by the BPCA DMC, the NICHD, and the FDA. The DMC will review data from individual study subjects on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study subjects. This evaluation will also assess data quality and timeliness, subject recruitment, accrual, and retention. These reviews will allow the DMC to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DMC to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided.

Ad Hoc Meetings of the DMC: The DMC may convene an ad hoc meeting to discuss any issue of safety raised by an investigator, the IND sponsor, or a member of the DMC. At the discretion of the investigators, the sponsor, and DMC members, a non-serious AE that is 1) associated with the product and 2) does not meet the stopping rules criteria may be considered as a trigger for an ad hoc DMC meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCC or Duke Clinical Research Institute (DCRI) sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations, the DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan Site visits will be made at standard intervals as defined by the clinical monitoring plans and may be made more frequently as directed by the IND and funding sponsors. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Study Outcome Measures

10.1.1 Primary Outcome Measures

1) PK parameters after multiple IV doses of clindamycin:
    - Clearance (Cl)
    - Volume of distribution (Vd)
    - Area under the curve (AUCtau)

10.1.2 Secondary Outcome Measures

1) PK results of patients transitioned to oral clindamycin:
    - Oral apparent clearance (Cl/F)
    - Oral apparent volume of distribution (V/F)

2) Safety: Adverse events will be collected during and after study drug administration.

10.2 Sample Size Considerations

It is anticipated that 12 children will be enrolled and treated in each of the IV groups for each age strata, leading to a total sample size of 24 subjects. A sample size of 24 subjects will provide adequate precision in the CL/F PK parameter estimate. Assuming an inter-individual 40% coefficient of variation in the population CL parameter estimate after weight-based allometric scaling, a sample size of 24 subjects would provide a margin of error of ± 16% in the 95% confidence interval of the CL estimate.

10.3 Analysis Plan

Population for Analysis
All subjects that receive at least 1 dose of study drug will be included in the safety analysis. All subjects with at least 1 evaluable PK sample will be included in the PK analysis n. If subjects have < 3 timed PK samples, additional subjects may be enrolled to ensure appropriate analysis.

Statistical Methodology
Descriptive statistics, such as number of observations, mean, median, 95% confidence interval, standard deviation, standard error, minimum, and maximum, will be presented by cohort for continuous variables (such as age, weight, and BMI). Other descriptive statistics, such as counts, proportions, and/or percentages, will be presented by cohort group to summarize discrete variables (such as race and sex).**Demographics and Baseline Characteristics**
The number of subjects completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be summarized. Variables include race, ethnicity, age, sex, and selected clinical variables recorded

prior to initiation of study drug. Study drug administration will be summarized by age and BMI cohorts.

Laboratory data, such as hematology and serum chemistry data, will be tabulated by age and BMI cohorts. Continuous laboratory measurements will be described using univariate 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.

Interim PK Analyses

An interim PK analysis of each age cohort will be performed after approximately 4 subjects have been enrolled into that cohort. If an interim analysis suggests that PK data is required on more than 12 subjects in that age cohort to evaluate the PK of clindamycin in this population, approximately 4 additional subjects will be enrolled into that age group for a total of 16 subjects.

PK Analysis

Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance. The influence of covariates (i.e., TBW, BMI, lean body weight, adjusted body weight, IBW etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each subject. The plasma concentrations-time profiles of clindamycin will be presented in figure form by subject and cohort (age and weight/BMI). Descriptive statistics will be presented for continuous and categorical variables. A detailed description of PK/PD analyses can be found in the PK analysis plan. We will compare PK parameters in this study of obese children to non-obese children.

11 SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in clinical trials. "Authorization" is required from each research subject (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the subjects' families. Consent forms describing in detail the study procedures and risks are given to the subject's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the subject's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject's legal guardian and answer any questions that may arise. The subject's legal guardian will sign and date the informed consent document prior to the subject being enrolled in the study. The subjects' legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects' legal guardians for their records. The rights and welfare of the subjects will be protected by emphasizing to their legal guardians that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the subjects' risk to receive the investigational product. This new information will be communicated by the investigator to subjects' legal guardians who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and subjects' legal guardians will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the subject consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed.

By signing the informed consent form, the subject's legal guardian agrees that the subject will complete all evaluations required by the trial, unless the subject is withdrawn voluntarily or is terminated from the trial for any reason.

12.1 Assent Process (e.g., Minor)

When a study includes subjects who may be enrolled in the study only with the consent of the subject's legally acceptable representative (e.g., minors), the subject should be informed about the study to the extent compatible with the subject's understanding. If capable, the subject should assent and sign and personally date the IRB-approved written assent form (if applicable based on local IRB guidelines). The assent form describes (in simplified terms) the details of the study, study procedures, and risks. Assent forms do not substitute for the consent form signed by the subject's legally acceptable representative. Consult with the institution's policies regarding enrollment of subjects who are unable to provide informed consent for themselves.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record subject data. The CRF will be used for the recording of all historical subject information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator. Data collection forms will be derived from the CRFs and provided by the DCC.

According to ICH E6, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file (regulatory binder) at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- MOP (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives,

microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the Principal Investigator, Pediatric Trials Network, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 50, 45 CFR 46 and 21 CFR 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

15.2 Institutional Review Board

Prior to its implementation, this protocol, including any subsequent amendments, the informed consent form, assent form, and any materials or advertisements presented to subjects, must be approved by an IRB constituted according to FDA regulations 21 CFR 56.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's federal-wide assurance number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Informed Consent

The investigator will choose subjects in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, a subject's parent/legal guardian will sign one informed consent for study enrollment. All subjects' parents/legal guardians must sign an informed consent form that complies with the requirements of both 21 CFR 50 and HIPAA before the subject enters the trial. A consent form that complies with the requirements of 21 CFR 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the subject's protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see **Section 12**.

15.4 Subject Confidentiality

Subjects will be assigned unique code numbers and will not be identified by name. Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. Clinical study sites will permit access to such records.

15.5 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments for 3 days following the last dose of study drug, unless there is an ongoing SAE for which the subject will be followed for up to 10 days after the last dose of study drug.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the CRFs and provided by the DCC to the sites to record and maintain data for each subject enrolled in the study that is not otherwise captured in the medical record. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the CRF should be consistent with the source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the source documents and CRFs.

16.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team in real time. The site data entry staff will ensure that they are accurate and complete, and will enter the data into AdvantageEDC^{SM} within 72 business hours of data acquisition. Serious adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee in real time, and entered into AdvantageEDC^{SM} within 24 hours of identification. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

16.2 Data Capture Methods

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

16.3 Types of Data

Data for this study will include demographic data, medical history, physical examination data including height/weight/BMI, safety, laboratory, and outcome measures including PK data.

16.4 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected quarterly.

16.5 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the Investigator for 10 years after the end of the study or per local/state regulations or until subjects reach 21 years of age, whichever is longer. Study information in a subject's medical records will be retained forever. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the PI when documents are no longer required to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the DCC's AdvantageEDC^{SM}.

A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB per their guidelines. The site principal investigator/study staff are responsible for knowing and adhering to their IRB requirements.

16.7 Subject Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in clinical trials. Authorization is required from each research subject (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 PUBLICATION POLICY

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

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

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research.

18 LITERATURE REFERENCES

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APPENDIX I

CDC Male and Female Child BMI Percentile Charts

APPENDIX II

A. PROHIBITED DRUGS for ALL subjects:

1) CYP 3A4 potent inhibitors including:
   a. Cyclosporine
   b. Erythromycin, clarithromycin
   c. Itraconazole, ketoconazole
   d. Ritonavir, delavirdine, protease inhibitors
   e. Nefazodone, fluoxetine, gluvoxamine
   f. Verapamil and diltiazem
2) CYP 3A4 inducers
   a. Rifampin,
   b. Phenytoin
   c. Ritonavir
3) Other: St. John's Wart

B. PROHIBITED DRUGS (unless the subject was receiving these drugs prior to enrollment and was receiving clindamycin as part of routine care prior to enrollment):

1) Neuromuscular blocking agents: Clindamycin may enhance neuromuscular blocking effect.
   a. Atracurium
   b. Cisatracurium
   c. Pancuronium
   d. Rocuronium
   e. Succinylcholine
   f. Vecuronium

APPENDIX III

Capsule Dosing Tables

WT_Low	WT_High		mg/kg/day_low	mg/kg/day_high	Goal	Total Daily Dose
20	20	150/150/150/150	30.0	30.0	30 mg/kg/day	600
21	30	300/300/300	30.0	42.9	30 mg/kg/day	900
31	40	300/300/300/300	30.0	38.7	30 mg/kg/day	1200
41	45	450/450/450	30.0	32.9	30 mg/kg/day	1350
46	60	450/450/450/450	30.0	39.1	30 mg/kg/day	1800
61	72	750/750/750	31.3	36.9	30 mg/kg/day	2250
73	80	600/600/600/600	30.0	32.9	30 mg/kg/day	2400
	>81	900/900/900				2700
20	25	300/300/300	36.0	45.0	40 mg/kg/day	900
26	32	300/300/300/300	37.5	46.2	40 mg/kg/day	1200
33	38	450/450/450	35.5	40.9	40 mg/kg/day	1350
39	48	450/450/450/450	37.5	46.2	40 mg/kg/day	1800
49	56	750/750/750	40.2	45.9	40 mg/kg/day	2250
57	64	600/600/600/600	37.5	42.1	40 mg/kg/day	2400
	>64	900/900/900				2700

APPENDIX IV

Clindamycin in Non-Obese Children

PO clindamycin:		*Dose 1*		*Dose 13*	*Dose 17*		
Dose Amount	Age range (years)	C_{max} (1 hour) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{max} (1 hour) (mcg/mL)	Half-life (h)	AUC (mcg/mL * h)
2 mg/kg	7-12	1.24 (0.70)	0.19 (0.27)	0.72 (0.21)	2.46 (0.68)	1.51 (0.74)	4.64 (2.11)
3 mg/kg	6-12	2.25 (0.53)	0.44 (0.19)	1.23 (0.31)	2.98 (0.93)	1.98 (0.60)	9.28 (2.71)
4 mg/kg	8-14	2.44 (0.65)	0.51 (0.25)	1.45 (0.36)	3.79 (0.61)	2.22 (0.78)	9.35 (3.23)
2 mg/kg	3-7	1.22 (0.51)	0.18 (0.23)	0.55 (0.17)	2.21 (0.51)	-	-
2 mg/kg	0.5-2	1.22 (1.14)	0.30 (0.37)	0.60 (0.32)	2.53 (0.86)	-	-
IV clindamycin:		*Dose 1*					
		C_{max}	Half-life (h)				
5-7mg/kg	"Pediatric Patients"	10	2.5				

* all values are means (standard deviation)
C_{max} – maximum concentration
C_{min} – minimum concentration
AUC – area under the concentration time curve

Pediatric Trials Network

Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLIN01

Phase I Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding Mechanism: Task Order

Protocol Number:	NICHD—2012-CLN01
Protocol Date:	03DEC-2012
Protocol Version:	2.0
IND Number:	115396 (P. Brian Smith, IND holder)
Principal Investigator:	Michael J. Smith, M.D., M.S.C.E. Assistant Professor of Pediatrics University of Louisville Louisville, KY 40202 Telephone: Redacted Fax: Redacted E-mail: Redacted

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to, 45 CFR 46 (Human Subjects Protection, incorporating Subpart D: Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D: Additional Safeguards for Children in Clinical Investigations), and 21 CFR 56 (Institutional Review Board [IRB]).

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

SITE PRINCIPAL INVESTIGATOR STATEMENT

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

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

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

Redacted

Principal Investigator Name (Print)

Redacted

Principal Investigator Signature

7 OCTOBER 2013

Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

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

Redacted

Pediatric Trials Network Study

Principal Investigator Name (Print)

Redacted

Principal Investigator Signature

7 OCTOBER 2013

Date

SUMMARY OF PROTOCOL CHANGES

The previous version of this protocol (version 1.0 dated 21 October 2012) was amended to create the current version (version 2.0 dated 03 December 2012). The table below provides the protocol history for this study.

Section Number(s)	Changes
Global Change	Changed protocol version from 1.0 dated 21 October 2012 to version 2.0 dated 03 December 2012
Global Change	Updated reference numbering
Global Change	Changed urine pregnancy test to serum pregnancy test
Cover Page	Updated IND holder to P. Brian Smith
Protocol Synopsis	Removed obese comparison from Objectives; clarified that dosing greater than 2.7g/day will be allowed for children receiving clindamycin as standard of care.
Study Event Table	Added waist:hip ratio; updated discarded scavenged samples
Section 1.0	Added IND Holder, P. Brian Smith contact information
Section 3.0	Removed obese/non-obese comparison from secondary aims
Section 5.2.1	Clarified duration of study participation
Section 6.1	Added waist:hip ratio
Section 6.2	Added language about site recruitment prior to IRB approval
Section 6.3	Added waist:hip ratio
Section 7.1.1	Clarified dose adjustment minimum for standard of care subjects
Section 7.1.2	Clarified dose adjustment limit to allow for standard of care subjects
Section 15.2	Added that protocol should be reviewed in accordance with subpart D of 45CFR46

Table of Contents

SUPPLEMENTS/APPENDICES

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BPCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cl	Clearance
Cl/F	Oral apparent clearance
CMP	Comprehensive Metabolic Profile
CRF	Case Report Form
CYP	Cytochrome
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mg	Milligram
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*
N	Number (typically refers to subjects)
NIH	National Institutes of Health
PD	Pharmacodynamics
PG	Pharmacogenomic
PK	Pharmacokinetics
PO	Oral
SAE	Serious Adverse Event
t1/2	Half-life
TBW	Total Body Weight
Vd	Volume of Distribution

V/F	Oral apparent volume of distribution

Protocol Synopsis

Protocol Title:	Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLIN01
Phase:	I
Product:	Clindamycin phosphate (intravenous) Clindamycin hydrochloride (oral capsules) Clindamycin palmitate (oral solution)
Objectives:	Primary: Determine the pharmacokinetics (PK) of intravenous clindamycin in overweight and obese children and adolescents Secondary: 1) Determine the PK of oral clindamycin in overweight and obese children and adolescents 2) Characterize the safety profile of clindamycin in overweight and obese children and adolescents
Study Design:	Prospective, multi-center, open-label, multiple-dose PK study of intravenous and oral clindamycin
Study Population:	Children ages 2 – < 18 years of age with body mass index (BMI) ≥ 85 percentile for age
Number of Subjects:	24–32 evaluable subjects
Number of Sites:	Up to 6 sites
Duration of Subject Participation:	Up to 18 days (1-day screening period, minimum of 2 doses prior to PK samples and maximum of 14-day treatment period, and 3-day observation period after study drug administration to monitor for serious adverse events)
Dose Schedule:	30–40 mg/kg/day dosed every 6 or every 8 hours with a maximum daily dose of 2.7 grams/day. Dosing greater than 2.7g/day will be allowed for children receiving clindamycin as standard of care.
Estimated Start:	October 2012
Estimated Time to Complete Enrollment:	Approximately 24 months
Inclusion Criteria:	1) 2 years – < 18 years of age at the time of first dose of study drug 2) Suspected or confirmed infection OR receiving intravenous clindamycin per routine care 3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug

	4) BMI ≥ 85th percentile for age and sex, based on CDC recommendations 5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)
Exclusion Criteria:	1) The following apply only to those who are NOT already receiving clindamycin as part of routine care: a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin b. History of *C. difficile* colitis with previous administration of clindamycin c. Aspartate aminotransferase (AST) > 120 units/L d. Alanine aminotransferase (ALT) > 210 units/L e. Total bilirubin > 3 mg/dL f. Serum creatinine > 2 mg/dL g. Receiving a neuromuscular blocker as part of therapy (see **Appendix II**) 2) Previous participation in the study 3) Subject is on prohibited medication or herbal product (see **Appendix II**) 4) Subject is receiving extracorporeal life support (ECLS) 5) Subject is post-cardiac bypass (within 24 hours) 6) Subject on inotropes/pressors 7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

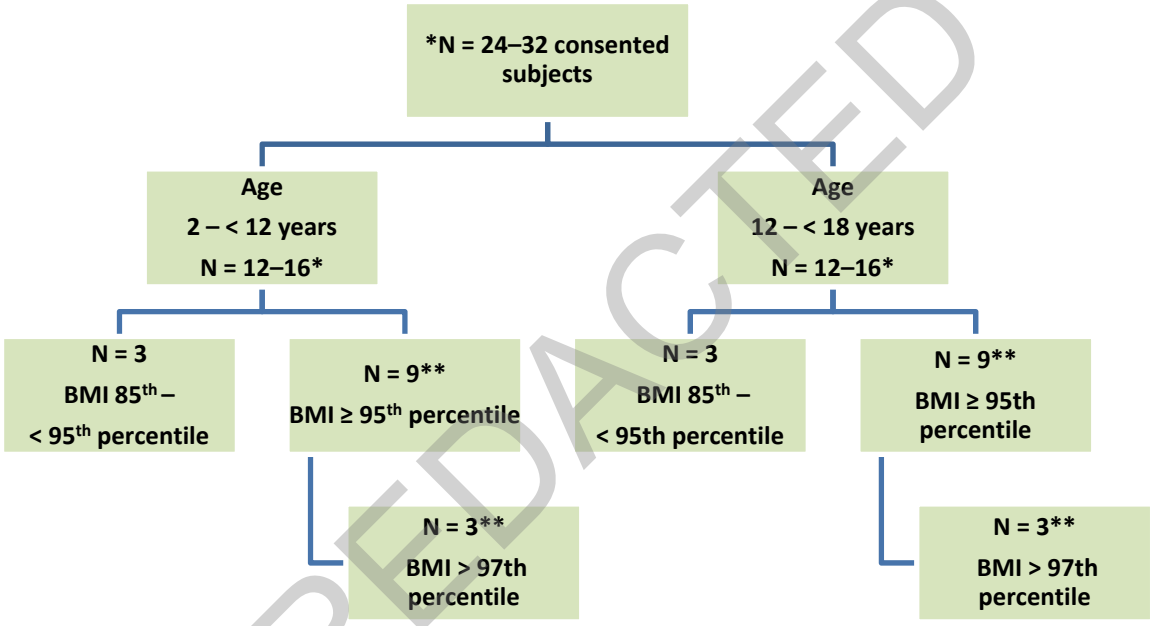
Table 1. Study Event Table

Study event/day	Screening/ study day 0	Study day 1 (any dose after the 1st dose of IV clindamycin; oral PK with 4th dose or later)	Study day 2–14	End of therapy OR early withdrawal or discontinuation	3-Day post-treatment phone follow-up
Informed consent/ assent & HIPAA	X				
Medical history	X				
Demographics	X				
Concomitant medications	X	X	X	X	X
Infection history	X	X			
Physical examination	X			X	
Weight	X				
Height	X				
BMI	X				
Waist:hip ratio	X				
Laboratory evaluation[a]	X			X	
α-1 glycoprotein (ELISA kit)[b]	X				
Laboratory evaluation (6.6.1 Table 2—if obtained as part of routine care)		X	X		X
Serum pregnancy test (female only)	X				
Feeding status (during PO PK portion only)		X			
Discarded scavenged samples[c]		X	X	X	
Clindamycin IV or PO[d]	X	X	X[f]		
PK samples[e]		X			
AE/SAE	X	X	X	X	X

[a]CBC, CMP.
[b]May be performed at any time during the study if not obtained at baseline.
[c]Discarded blood cells may be collected at any time during the study.
[d]Group assignment (see Figure 1).
[e]PK sampling (Table 3, see Section 6.6.2).

[f]IV clindamycin will be continued per treating physician; when switched to PO, subject will participate in PO PK study.

Figure 1. Schematic/Description of Study Design



*IV subjects who transition to oral clindamycin will participate in the oral PK study.
**Minimum of 3 subjects with BMI > 97th percentile in each age group.

1 KEY ROLES

For questions regarding this protocol, contact:

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Over the past decade, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a leading cause of hospitalization for children and adolescents in the United States (1). Consequently, the use of antimicrobial agents active against MRSA has become more prevalent (2). Specifically, the use of clindamycin among children hospitalized with *Staphylococcus aureus* infections increased from 21% in 1999 to 63% in 2008. At the same time, rates of childhood obesity have continued to remain high. Recent national data demonstrate that 17% of children aged 2–19 years in the United States are obese (body mass index [BMI] ≥ 95th percentile) and 12.3% are morbidly obese (BMI ≥ 97th percentile) (3). Obese patients have a greater likelihood of complications from infectious diseases and are at increased risk of developing *Staphylococcus aureus* infections. Therefore, an understanding of the PK of clindamycin in this population is critical to ensure appropriate interventional therapy.

Clindamycin, a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin (4), is approved by the U.S. Food and Drug Administration for the treatment of pediatric and adult patients with respiratory tract, female pelvis and genital tract, and skin and soft tissue infections with susceptible bacteria including streptococci, pneumococci, and staphylococci. Clindamycin is also approved in adults for septicemia and intra-abdominal and serious infections with susceptible anaerobic bacteria (5).

Clindamycin is approximately 90% protein-bound. It is metabolized by the liver and excreted via the liver, bile, and kidneys. Impaired renal function modestly decreases the elimination of clindamycin; however, dosage adjustment is not required with renal dysfunction (4). Clindamycin phosphate (intravenous [IV] formulation) is rapidly converted to active clindamycin which has an elimination half-life of about 3 hours in adults and 2.5 hours in children (5). The drug penetrates well into all tissues, with the exception of the brain and cerebral spinal fluid. It is actively taken up and concentrated within the phagocytic cells. Clindamycin binds to the 50S subunit on the bacterial ribosome and inhibits protein synthesis by interfering with the formation of initiation complexes, thus inhibiting exotoxin production (4). Clindamycin exhibits time-dependent killing; and efficacy is correlated with the time clindamycin concentrations exceed the minimum inhibitory concentration of the pathogen of interest. A summary of clindamycin serum concentrations in non-obese children is found in Appendix IV.

Variability in serum and tissue concentrations has been reported in obese patients (4). The underlying premise is that this is due to physiologic changes that alter a drug's volume of distribution (Vd) and body clearance (Cl) (6,7). Thus, obese patients may be dosed inappropriately if fixed or "adult" doses are used (under-dosed) or if weight-based dosing is used (over-dosed) (6,7). Because critically ill obese patients with infections are reported to have a worse outcome than non-obese patients (8), it is imperative to determine if the disposition of and response to clindamycin may be altered compared to healthy children with an infection. In addition, sub-therapeutic drug concentrations may increase the development of resistant organisms. Thus, it is important to perform pharmacokinetic (PK) and pharmacodynamic (PD)

studies in the obese pediatric population to ensure that these patients are being optimally dosed with medications designed to treat infections. There are no currently available PK (or PD) data to guide clindamycin dosing in obese pediatric or adult patients. This proposal will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years.

2.2 Scientific Rationale

Selection of the correct drug dose and dose regimen is the most important decision in ensuring optimal pharmacotherapy. Defining an optimal regimen requires a clear understanding of the drug's PK, PD, and, for many compounds, pharmacogenomic (PG) profiles. Understanding these characteristics for drugs used in pediatrics is imperative to determine optimal dose regimens across the pediatric age continuum.

Clinically, drug dosing in pediatrics is individualized to age by basing the drug dose on a patient's body weight and the dose interval on the functional capacity of the drug's clearance pathways. This approach assumes, though inaccurately, that a drug's Vd and body Cl are directly proportional to a patient's body weight. Despite this lack of proportionality, the majority of pediatric patients favorably respond to weight-based drug dosing. However, as the potency of newer drugs increases and the need for more precise drug dose regimens expands, better-defined dose regimens based on careful assessment of the drugs' integrated PK-PD-PG profiles across the pediatric age continuum are needed (9). Complicating this paradigm are the substantially increasing numbers of children and adolescents who are obese, and even morbidly obese, and the lack of data on disposition in the obese population. Clinical trials of new drugs focused on FDA labeling exclude obese patients, leaving the determination of dosing regimens in the obese for post-marketing, often investigator-initiated studies.

Antibiotic Dosing Regimens Based on PK-PD Modeling
Prior to our understanding of the integrated PK-PD characteristics for antibiotic drugs, antibiotic dosing regimens were mostly based on perceived maximum tolerated doses often related in some manner to the target pathogen minimum inhibitory concentration (MIC). Integration of an antibiotic's PK with PD allows for the determination of the optimal dose regimen across the spectrum of antibiotic drugs (10,11). In addition, this more quantitative approach permits comparisons of different antibiotic drugs for a specific infection and far more accurate predictability of patient response. The specific antibiotic PK-PD characteristic used to predict outcome (i.e., bacteriologic eradication) appears to be mostly dependent on whether the drug's bacterial killing is concentration- or time-dependent. Clindamycin is most often described as a "time-dependent antibiotic with moderate persistent effects," and as such, the best predictor of bacterial killing appears to be the ratio of the area under the clindamycin (free, unbound) drug concentration time curve (AUC) divided by the targeted pathogen MIC (i.e., fAUC/MIC) (11). To accurately determine this pivotal PK-PD parameter, what is needed is a comprehensive understanding of the drug's PK profile across the age spectrum while incorporating the spectrum of pathophysiologic changes and differing body habitus. For clindamycin, these data are not available.

Clindamycin Pharmacokinetics
Limited published clindamycin PK data exist and encompass < 100 neonates, infants, and children. In neonates, clindamycin elimination is delayed compared with older infants and children—mean elimination half-life (t ½) values of 8.7 vs. 3.6 hours, respectively (12,13).

Regardless of age group studied, variability was observed in clindamycin t ½, Vd, AND systemic Cl. In addition, some studies report variable serum clindamycin concentrations (bioactivity) following parenteral dosing (12,14). Despite this variation in drug disposition, which is observed in both children and adults, bioactive serum clindamycin concentrations remain therapeutic following routine parenteral (intramuscular [IM], IV) or oral dosing. Considering that clindamycin, an antibiotic, is used to treat infections caused by susceptible pathogens responsible for infectious diseases regardless of patient age, pediatric clindamycin development strategies need only focus on the drug's safety and PK profile to ensure similar systemic exposure. Available clindamycin PK data support close similarity for clindamycin systemic exposure (i.e., bioactive serum clindamycin concentrations and AUC) in older infants, children, and adults following comparable mg/kg doses (12, 14-191). As noted above, clindamycin PK in premature and full-term infants is, as expected, different than that observed in older patients (12,13). This foundation of data underscores the importance of studying clindamycin disposition in the obese pediatric patient.

Clindamycin is extensively bound to plasma protein, primarily to alpha 1 acid glycoprotein, and, with the exception of the brain or cerebrospinal fluid, effectively penetrates body tissues and fluids. The drug is metabolized primarily by the cytochrome (CYP) P450 isoenzyme CYP3A4 to two primary, antimicrobial active metabolites, a sulfoxide and to a lesser extent N-demethylclindamycin (20). Although only limited data are available for current clindamycin pediatric dosing regimens, the regimens employed clinically have been used for decades with apparent success. Nevertheless, clindamycin optimal dosing regimens in pediatrics remain unknown. Furthermore, the influence of obesity on clindamycin disposition is unknown and may have a far greater negative impact on patient outcome due to ill-defined, clinically extrapolated dosing.

Drug Dosing and Obesity

Data defining optimal drug dosing in the obese and morbidly obese adult patient are very limited and virtually non-existent in pediatrics. Drug dosing on total body weight (TBW) in the obese patient has the real risk of overdosing the patient, resulting in an increased incidence of adverse effects, while dosing on ideal body weight (IBW) can lead to serious under-dosing. In obese adults, IBW is increased by 20–40%, which is unaccounted for when using the many mathematical formulas available to calculate dosing based on a person's IBW. This deficiency may partially explain the inaccuracy of drug dose regimens for obese patients based on IBW formula estimations (21–26).

The influence varying degrees of obesity have on important physiologic functions across the age continuum in pediatrics is unknown. In adults, sparse data suggest that obese adults may have altered tissue blood flow rates due to inherent differences in blood flow to lean (greatest amount) and adipose tissue, impaired cardiac function, and alterations in phase I and II metabolism. Although intuitive, one might assume that a drug's Vd would be increased in obese patients for lipophilic compounds, though in fact, for the few drugs assessed, the Vd is highly variable. Similarly, Cl is also highly variable in the obese population, underscoring the need to determine drug disposition characteristics not only across the age continuum but also with increasing degrees of obesity (21–24). No such data are available for the pediatric patient, but these data combined underscore the need to critically assess a drug's disposition relative to age and body habitus. Furthermore, for antibiotics whose efficacy is dependent on achieving effective concentrations at the infectious site, interfaced with the organism, optimal dosing in the obese pediatric patient must be defined (6,7).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of Blood Draws
There are small risks to blood sampling, usually some pain/discomfort with the blood stick. Every effort will be made to avoid additional (to standard of care) sticks for this study by timing clinical blood draws to coincide with timed samples when possible and the use of existing IV lines when feasible for the blood draws.

Risks of Clindamycin
From the FDA label and review of the literature, the following are adverse reactions of clindamycin: antibiotic-associated colitis, pseudomembranous colitis, abdominal pain, nausea, and vomiting; hypersensitivity reactions (maculopapular rash and urticaria have been observed during drug therapy; generalized mild-to-moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions; rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin; a few cases of anaphylactoid reactions have been reported). Organ systems that are affected include skin and mucous membranes (pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported); liver (jaundice and abnormalities in liver function tests have been observed during clindamycin therapy); renal system (although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances); hematopoietic (transient neutropenia [leukopenia] and eosinophilia have been reported; reports of agranulocytosis and thrombocytopenia have been made; no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances); local reactions (pain, induration, and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion); musculoskeletal (rare instances of polyarthritis have been reported); cardiovascular (rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV administration). There is minimal additional risk to the subjects who are receiving clindamycin as part of their routine medical care.

2.3.2 Known Potential Benefits

The subject may benefit from the use of the study drug; however, participation in this study has no other potential benefits to the subjects. The results of this study may benefit overweight and obese subjects in the future who require clindamycin therapy.

3 OBJECTIVES

Primary Aim
Characterize the PK of multiple-dose IV clindamycin in overweight and obese children and adolescents.

Secondary Aims
1. Characterize the PK of multiple-dose oral clindamycin in overweight and obese children and adolescents.
2. Characterize the safety profile of clindamycin in overweight and obese children and adolescents.

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1. PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUCtau)

3.1.2 Secondary Outcome Measures

1. PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2. Safety profile: Adverse events will be collected during and after study drug administration..

4 STUDY DESIGN

This will be a prospective, open-label PK and safety profile study of multiple doses of IV and oral clindamycin in overweight and obese children 2 – < 18 years of age. The total study duration is expected to be approximately 24 months; each subject will participate in the study for up to 18 days (screening day; treatment days 1–14 [may be as short as 2 days] followed by an observation period of 3 days post discontinuation of clindamycin therapy or after day 17 (on day 18) of therapy in those who are treated with more than 14 days of clindamycin).

5 Study Population

Selection of the Study Population

Eligible subjects ages 2 – < 18 years will be identified through the inpatient units at each participating site. There will be up to 32 evaluable subjects (defined in Section 10.3) enrolled; however, target enrollment will be 24 subjects. If dosing changes are suggested by the interim PK analysis (see **Section 10.3**), approximately 8 additional subjects will be enrolled. Twelve to 16 subjects will be enrolled in each of the following age groups: 2 – < 12 years and 12 – < 18 years of age. Subjects will be further stratified into 1 of 2 groups based on their BMI (85^{th} – < 95th percentile, and ≥ 95th percentile). No more than 3 subjects with BMI in the 85^{th} – < 95th percentile will be enrolled in each age group. Participating sites will prioritize enrollment of subjects with BMI > 97^{th} percentile in each age group.

5.1 Inclusion/Exclusion Criteria

The investigator or other study site personnel will document in the source documents (e.g., the hospital chart) that informed consent and assent (if applicable) were obtained. Laboratory tests or non-pharmacologic treatment procedures that were performed and considered "routine care" within 72 hours of first dose of study drug may be used for screening procedures required by the protocol and recorded in the case report form (CRF).

Inclusion Criteria

1) 2 years – < 18 years of age at the time of first dose of study drug
2) Suspected or confirmed infection OR receiving IV clindamycin per routine care
3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug
4) BMI ≥ 85^{th} percentile for age and sex, based on CDC recommendations
5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

Exclusion Criteria

1) The following apply only to those who are NOT already receiving clindamycin per routine care:
   a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin
   b. History of *C. difficile* colitis with previous administration of clindamycin
   c. AST > 120 units/L
   d. ALT > 210 units/L
   e. Total bilirubin > 3 mg/dL
   f. Serum creatinine > 2 mg/dL
   g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II**)
2) Previous participation in the study
3) Subject is on prohibited medication or herbal product (see **Appendix II**)
4) Subject is receiving extracorporeal life support (ECLS)

5) Subject is post-cardiac bypass (within 24 hours)
6) Subject on inotropes/pressors
7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

5.2 Treatment Assignment Procedures

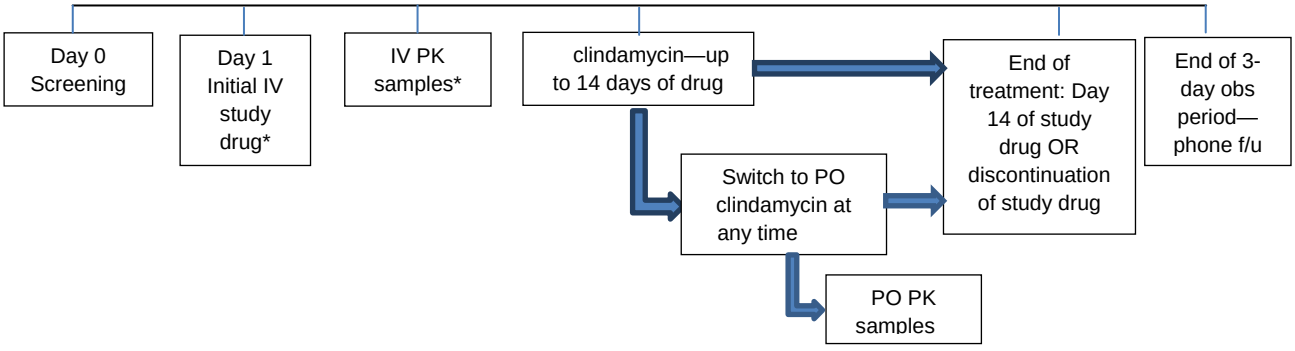
This will be an open-label PK study. Subjects will be assigned to age groups based on age upon first dose of study drug and to a BMI group based on BMI at study entry.

5.2.1 Duration of Study Participation

Duration of therapy will be up to 14 days for children who receive the first dose of clindamycin as the study drug. All subjects will begin on IV therapy and must receive at least 2 doses of IV clindamycin to participate in the study. The total duration of therapy with clindamycin will be determined by the treating physician for those children who are receiving clindamycin as part of routine care; however, only 14 days of therapy from the time of enrollment will be considered as study drug. If therapy extends beyond 14 days, the study follow-up visit/call will occur on day 18 (after completion of 3 safety observational days [72–96 hours]). Patients who are receiving antimicrobial agents other than clindamycin may enroll in this study and receive up to 3 doses of IV clindamycin and 4 doses of oral clindamycin in addition to their standard of care therapy. Subjects who transition to oral clindamycin may return as outpatients to complete the PK portion of the study.

Total duration of study participation will be up to 18 days. This will comprise a 1-day screening period; a minimum 2 doses of IV and 4 doses of oral clindamycin before PK sampling begins for IV and oral routes, respectively; a maximum 14-day treatment period; and a 3-day post-study observation period to monitor for serious adverse events. The 3-day post-treatment visit may be a phone follow-up. Patients may continue clindamycin per their physician's recommendation after they have completed participation in this (maximum of) 18-day study.

Figure 2.Timeline



*Minimum of 2 doses of IV clindamycin before IV PK period.

**Minimum of 4 doses of PO clindamycin before PO PK period.

5.2.2 Replacement Subjects

Subjects in the IV portion of this study who are unable to provide at least 3 timed PK samples may be replaced.

5.2.3 Reasons for Subject Withdrawal

A subject or his/her parent/guardian may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time. Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject or investigator noncompliance with the study protocol
- At the request of the subject, investigator, treating physician, or sponsor
- Adverse reaction or suspected adverse reaction.

Subjects are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. The subject who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations, and will be provided appropriate care under medical supervision until the symptoms of any adverse event (AE) resolve or the subject's condition becomes stable. Subjects withdrawn from the study due to an AE must be followed per protocol (see **Section 8.2.4**).

5.2.4 Termination of Study

This study may be terminated at any time by NICHD, the Investigational New Drug Application (IND) sponsor, or the Data Monitoring Committee (DMC) if serious adverse reactions occur in 2 or more subjects that are directly related to study drug, or if, in NICHD's judgment, there are no further benefits to be achieved from the study. A study site may be terminated if the investigator does not adhere to the study protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

See the schedule of study events and procedures on page xi (**Table 1**).

1. Medical history will be obtained by interview with the parent/legal guardian/subject and from the subject's medical records.

2. Concomitant medications of interest administered within 72 hours prior to and during the period of administration of study drug, including herbal products of interest, will be recorded (see **Appendix II**).

3. Physical examination, including abnormal physical findings, height (measured standing if possible), weight and waist:hip ratio will be obtained. BMI will be calculated from height and weight using the following formula: BMI = [weight (kg) / (stature (cm))^2] x 10,000. Please refer to the website for the Centers for Disease Control (CDC) pediatric BMI calculator (http://apps.nccd.cdc.gov/dnpabmi/). The BMI percentile will be obtained using the BMI calculator and verified using the age- and sex-specific CDC BMI charts (**Appendix I**).

4. The safety laboratory testing complete metabolic panel (CMP) and complete blood count (CBC) will be performed at each site's local laboratory. Baseline CMP and CBC may be used if obtained as part of routine care within 72 hours prior to study enrollment. The serum pregnancy test will also be performed at the local laboratory (within 24 hours prior to study enrollment). Alpha-1-glycoprotein will be measured using an ELISA kit (central laboratory) at one time point after consent.

5. PK samples will be obtained with the second or subsequent doses of clindamycin for IV PK samples and after 4 doses of oral clindamycin (see **Section 6.6.2**).

6.2 Screening

Research staff at sites will screen potential subjects for eligibility requirements. A partial waiver will be completed with the IRB submission at each site to allow for screening of potential subjects prior to obtaining informed consent. Site staff may employ IRB-approved recruitment efforts prior to the subject consenting but an informed consent form must be signed before any protocol-specific procedures are performed to determine eligibility.

6.3 Enrollment/Baseline

Baseline/Pre-Dose Assessment (Day 0)
After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA documents, the subject has signed assent (if applicable), and after it has been determined that

the subject satisfies all inclusion and no exclusion criteria, the following evaluations will be performed and recorded in the CRF:

1. Subject demographics
2. Physical examination, including weight, height, waist:hip ratio and BMI
3. Pertinent medical history
4. Concomitant medications (72 hours prior to first dose of study drug)
5. Laboratory determinations (see **Table 2, Section 6.6.1**)
6. Culture results of blood, urine, sputum, or wound (if obtained as part of routine care) within 72 hours prior to the first dose of study drug
7. For subjects receiving clindamycin per routine care, the date and time for the doses administered prior to first dose of study drug will be recorded (up to a maximum of 6 prior doses)
8. Serum pregnancy test (females only who have reached menarche) within 24 hours of study enrollment

Assessments/Procedures (Days 1–14)
The subject will start study drug upon completion of the pre-assessment, or, if s/he was already receiving clindamycin (at the study-recommended dose), s/he will continue receiving that dose of clindamycin. If s/he was receiving clindamycin at a dose lower than the study-recommended dose, the dose will be changed to be in compliance with the protocol. Total body weight will be used to calculate the absolute dose administered. Refer to **Section 7.1.2** for dosing. Subjects who transition to oral therapy will participate in the oral-dose PK portion..

The following assessments will be conducted after the subject receives the first dose of clindamycin after study enrollment and throughout therapy up to day 14:

1. Concomitant medications of interest (see **Appendix II**)
2. Start date/time and stop date/time of clindamycin administration and flush date/stop time after IV administration
3. Feeding status (during PO PK portion only): NPO, clear liquids, full feeds, etc.
4. Collection of PK samples (including date/time); see **Section 6.6.2**
5. Laboratory results for laboratory tests of interests (see **Section 6.6.1**)
6. Collection of culture results (if available)
7. Adverse events (see **Section 8.2.1**)

6.4 End of Therapy OR Early Withdrawal/Discontinuation

The following assessments will be conducted at early withdrawal or end of therapy:

1. Concomitant medications of interest (see **Appendix II**)
2. Physical examination
3. Laboratory evaluations (see **Section 6.6.1**)
4. Adverse events (see **Section 8.2.1**)

6.5 Follow-up Safety Phone Call

Assessments/Procedures (Day 3 Post Treatment): This visit will be a phone follow-up unless the subject is still hospitalized. This assessment must occur at least 72 hours but no more than 96 hours after the last dose of study drug. The following information will be obtained:

1. Adverse events (see **Section 8.2.1**)
2. Concomitant medications
3. Any labs collected

6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

The safety laboratory testing (CMP and CBC) will be performed in the local laboratory at each site. CMP and CBC performed as part of routine care within 72 hours prior to enrollment may be used for baseline laboratory tests. A CBC and CMP will be obtained at the end of therapy (any hematology or chemistry values obtained within ± 24 hours of discontinuation of study drug or within ± 24 hours of completion of 14 days of study drug (if they are continuing clindamycin beyond 14 days) may be used as end-of-treatment laboratory values). If these laboratory tests have not been performed as part of routine care, they will be performed for the study per the protocol schedule. The serum pregnancy test will also be performed at the local laboratory. Alpha (α)-1-glycoprotein will be performed once during the study using an ELISA kit (central laboratory).

Table 2. Laboratory Evaluations

Hematology	Serum Biochemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Platelets	Chloride
White blood cells	Bicarbonate
	Total calcium
	Glucose
	Creatinine
	Blood urea nitrogen
	Total protein
	Albumin
	Aspartate aminotransferase
	Alanine aminotransferase
	Bilirubin
	α-1 glycoprotein (central laboratory)

6.6.2 Special Assays or Procedures

PK Samples
Blood (0.5 mL) will be collected with scheduled IV and oral doses of clindamycin for clindamycin plasma concentration determinations (see **Table 3** below for schedule). In subjects receiving IV clindamycin, PK samples should be collected from a site separate from the site of administration. PK samples in subjects on IV clindamycin will be collected with any dose after the first dose of study drug (excluding the first dose), and, for PO clindamycin, PK samples will be collected with the fourth dose or any dose after the fourth dose. The PK sampling will be drawn according to the following schedule relative to the end of infusion (IV PK) or actual time of oral administration (PO PK).

Table 3. PK Schedule

Scheduled PK Sampling Times				
Time (hours)*	**IV dose***		**PO dose**	
	Q6h	**Q8h**	**Q6h**	**Q8h**
Pre-dose 0 (within 15 minutes prior to the dose)	**X****	**X****	**X****	**X****
0.5 (± 5 minutes)	**X****	**X****	N/A	N/A
1–1.5	X	X	**X****	X**
3–4	**X****	**X****	**X****	--
5–6	--	X	--	**X****
Pre-dose (will depend if on q6h or q8h dose schedule)	**X****	**X****	**X****	**X****
Total number of samples	5	6	4	4

* Time starts at end of flush after the 30-minute infusion.
** Priority samples (see paragraph below).

Every effort should be made to collect all PK samples for each subject. Collection of PK samples should be timed with collection of laboratory tests per standard of care to minimize blood draws specifically for the study. If it is impractical to collect all PK samples during the same dosing interval, samples can be obtained at different dosing intervals. If it is impossible to obtain all PK samples for each subject, **PK samples can be prioritized to include:**

a) **For IV administration: pre-dose, 0.5 hours, 3–4 hours, and pre-next dose**
b) **For oral administration: pre-dose, 1–1.5 hours, 3–4 hours (q6h dosing), 5–6 hours (q8h dosing), and pre-next dose**

Clindamycin concentrations in plasma will be measured at a central laboratory using a validated bioanalytical assay. In addition, scavenged samples will be obtained.

Scavenged Plasma Sampling
Plasma samples collected in EDTA tubes during the course of therapy (~100 µL plasma or ~200 µL whole blood) will be procured, after consent. A maximum of 10 scavenged plasma samples will be collected per subject. Collection may begin with any specimen collected after the first dose of study drug through 24 hours after the last dose of study drug. The date and time of

sample collection, as well as the date and time the sample is frozen, will be collected for all scavenged samples.

Minimizing Blood Loss
To minimize the amount of blood sampling, hematology and chemistry laboratory measures will be obtained only at baseline and end of study. If they have been obtained as part of routine care within 3 days prior to enrollment into the study, the baseline CMP and CBC do not need to be repeated. The PK sampling scheme will be employed such that no more than a total of 8 mL (< 3 mL/kg) of blood is obtained from each subject for PK analysis. Plasma samples will be collected in 0.5 mL blood aliquots.

6.6.3 Specimen Preparation, Handling, Storage, and Shipping

Detailed information for collection, labeling, preparation, handling, storage, and shipping of specimens is detailed in the manual of procedures (MOP).

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

A dose of 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 g/day is selected based on current labeling. Patients who are receiving clindamycin as part of their routine care are also eligible to participate if their dose can be adjusted to be at least 30 mg/kg/day upon enrollment. The dose administered will be based on TBW. Because bioavailability is estimated at 85%, the same dose will be used for oral administration as is used for IV dosing. Both solution and capsule preparations will be included in this study because both oral formulations are utilized in clinical practice, and it will allow the inclusion of those patients who cannot swallow pills. In the absence of PK data, we assume that drug clearance will be comparable in obese pediatric patients compared to non-obese pediatric patients. Therefore, a dosing regimen 30–40 mg/kg per day and a maximum dose of 2.7 g/day should provide exposures similar to those used in children and adolescents with a normal BMI. It is predicted to be safe in the obese population because similar doses are currently used per routine care.

7.1.2 Dose and Timing

Both q6h and q8h dosing will be allowed for both oral and IV dosing of clindamycin. For children receiving clindamycin as part of clinical care, this protocol will not prescribe a route of administration or dosing interval; the dose, route of administration, and dosing interval prescribed by the treating physician will be recorded on the CRF. Dosing greater than 2.7g/day will be allowed for children receiving clindamycin as part of clinical care. However, if the prescribed dose is less than the lowest dose for this study, the dose of clindamycin will be changed to comply with the study-recommended dose. See **Section 5.2.1** for duration of therapy.

IV dosing: A minimum of 2 doses of IV clindamycin will be administered. The dose administered will be based on TBW at 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 grams/day. The drug will be administered over 30 minutes. The venous access line will be flushed per local practice of the completion of IV administration, and the time of the end of flush will be documented.

Oral dosing: For those subjects who are receiving clindamycin as a solution, they will receive 30–40 mg/kg/day divided q6h or q8h. For those subjects receiving the capsule formulation, they will receive the dose of clindamycin defined in **Appendix III**. Only whole capsules will be used. The oral solution will be used for those subjects who cannot swallow capsules. During the PO phase of the study, PK samples should be obtained with the fourth dose of PO clindamycin (but may be collected with a later dose if unable to do the fourth dose). No more than 12 PO study drug doses will be administered as part of this study.

7.1.3 Formulation, Packaging, and Labeling

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules.

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles for reconstitution.

Each formulation is approved for use in the United States.

7.1.4 Product Storage and Stability

Clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules), and clindamycin palmitate (PO oral solution) will all be stored at room temperature (20–25^0 C). Diluted clindamycin phosphate (IV) is stable at room temperature for at least 16 days and refrigerated for at least 32 days. Reconstituted clindamycin palmitate hydrochloride, USP for oral solution is stable for 2 weeks at room temperature and should not be refrigerated. See the MOP for detailed information.

7.2 Preparation and Administration of Study Intervention/Study Drug

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL. The drug will be infused over 30 minutes. Infusion rates should not exceed 30 mg/minute. The pharmacy will prepare the IV formulation, and the dose administered will be based on TBW.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules, and the dose will be dispensed based on TBW (see **Appendix III** for dosing).

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles and will be prepared in the pharmacy at each site based on the reconstitution recommendation in the label. The dose administered will be based on TBW.

Refer to the MOP for additional details regarding drug procurement, drug preparation, and administration.

7.3 Modification of Study Intervention/Investigational Product for a Subject

No dosing adjustments are required for hepatic or renal impairment.

7.4 Accountability Procedures for the Study Intervention/Study Drugs

Each site will provide drug for their study subjects. The study product accountability records will be maintained in the pharmacy study binder for clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules) and clindamycin palmitate (PO oral solution). See MOP for specific details related to investigational product accountability.

7.5 Assessment of Subject Compliance w/ Study Intervention

Compliance with dosing will be determined using the pharmacy accountability logs and the subject's medication administration record. For those subjects who are discharged on oral clindamycin and have not completed the PO PK visit, the subject will keep a drug administration diary and all drugs will be accounted for at the outpatient PK study visit.

7.6 Concomitant Medications/Treatments

Prohibited drugs are listed in **Appendix II**.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

AEs will be collected during and after study drug administration and for 3 days following end of therapy with clindamycin. Results will be tabulated by MedDRA System Organ Class and Preferred Term.

8.2 Methods & Timing for Assessing, Recording, & Analyzing Safety Parameters

AEs will be collected from the time of consent, throughout the period of study drug administration, and for 3 days following end of therapy with clindamycin. See **Section 8.6** for clarification for AEs identified at the 3-day follow-up visit and for serious AEs (SAEs). Safety will be assessed by frequency and incidence of AEs and SAEs. The Best Pharmaceuticals for Children Act (BPCA) safety monitoring committee (DMC) convened by NICHD will review data and safety information from study subjects.

8.2.1 Adverse Event

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

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

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

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

1. Death
2. Life-threatening AE (“life-threatening” means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.2.2 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, investigational plan, or informed consent.

8.2.3 Identification of Events and Timeframe for Reporting

As all subjects in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after consent has been obtained. The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome. Any event beginning more than 3 days after the last dose of study drug will not be captured.

8.2.4 Follow-up of Adverse Events

AEs ongoing at the time of the last dose of study drug will be followed up to 3 days after the last dose of study drug. AEs that resolve during the study or follow-up period will have the resolution date documented in the CRF. Adverse events that are identified at the last assessment visit/phone contact (or at the early termination visit) must be recorded on the AE CRF, with the status of the AE noted. Any events that are identified at the last assessment visit/phone contact will be followed for an additional 3 days for AEs and 10 days for SAEs and if still ongoing can be "resolved by convention". All serious suspected adverse reactions will be followed until resolution. All enrolled subjects in both cohorts who receive at least 1 dose of clindamycin will be followed for safety.

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Subject is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. **MODERATE**: Subject experiences enough symptoms or findings to require intervention

3. **SEVERE**: Subject experiences symptoms or findings that require significant intervention

8.4 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction. ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.5 Reporting Procedures and Timeframe for Reporting

All AEs will be entered into the data system within 72 business hours of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties encountered when entering the event into the electronic data capture (EDC) system, the SAE will be reported to the data coordinating center (DCC) by telephone or FAX communication. Investigators must submit safety reports as required by their local IRB, independent of the reporting requirements specified in the protocol.

8.5.1 Serious Adverse Events

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC, IND sponsor, and funding sponsor (NICHD). The BPCA DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.5.2 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The sponsor or his representative will submit expedited safety reports (IND safety reports) to the FDA and other regulatory agencies as necessary, and will inform the DMC and investigators of such regulatory reports. Site investigators must submit IND safety reports as required by their IRB. Documentation of the submission to and receipt by the IRB should be retained for each IND safety report. The sponsor will submit a progress report of the investigation annually, which will include a summary showing the most frequent and most serious adverse events by body system.

8.6 Type and Duration of Follow-up of Subjects after Adverse Events

Adverse events will be followed by the investigator or a clinician member of the study team in person if the subject is hospitalized for an AE or SAE. If the subject is not hospitalized, the investigator or a clinician may review the subject’s medical record, contact the subject by phone, or contact the subject’s primary care physician for follow-up.

Subjects withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator. Refer to Section 8.2.4 for follow-up of AEs/SAEs. The medical monitor or study principal investigator must be notified if the AE may relate to overdose of study treatment.

8.7 Halting Rules

Subject safety data will be reviewed on an ongoing basis to monitor for halting criteria.

The study enrollment and dosing will be halted for a safety review by the BPCA DMC if serious adverse reactions occur in ≥ 2 subjects.

Furthermore, the NICHD, the IND sponsor, the DMC, and the investigators shall have the right to recommend termination of this study at their discretion. Possible reasons for termination of the study include, but are not limited to:

1. Adverse events
2. Unsatisfactory enrollment with respect to quantity or quality

The study may be placed on hold or terminated at a site(s) for the following reasons:

1. Inaccurate or incomplete data collection
2. Falsification of records
3. Failure to adhere to the protocol

8.8 Safety Oversight (Safety Monitor plus DMC)

This study will be overseen by the BPCA DMC, the NICHD, and the FDA. The DMC will review data from individual study subjects on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study subjects. This evaluation will also assess data quality and timeliness, subject recruitment, accrual, and retention. These reviews will allow the DMC to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DMC to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided.

Ad Hoc Meetings of the DMC: The DMC may convene an ad hoc meeting to discuss any issue of safety raised by an investigator, the IND sponsor, or a member of the DMC. At the discretion of the investigators, the sponsor, and DMC members, a non-serious AE that is 1) associated with the product and 2) does not meet the stopping rules criteria may be considered as a trigger for an ad hoc DMC meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCC or Duke Clinical Research Institute (DCRI) sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations, the DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan Site visits will be made at standard intervals as defined by the clinical monitoring plans and may be made more frequently as directed by the IND and funding sponsors. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Study Outcome Measures

10.1.1 Primary Outcome Measures

1) PK parameters after multiple IV doses of clindamycin:
    - Clearance (Cl)
    - Volume of distribution (Vd)
    - Area under the curve (AUCtau)

10.1.2 Secondary Outcome Measures

1) PK results of patients transitioned to oral clindamycin:
    - Oral apparent clearance (Cl/F)
    - Oral apparent volume of distribution (V/F)

2) Safety: Adverse events will be collected during and after study drug administration.

10.2 Sample Size Considerations

It is anticipated that 12 children will be enrolled and treated in each of the IV groups for each age strata, leading to a total sample size of 24 subjects. A sample size of 24 subjects will provide adequate precision in the CL/F PK parameter estimate. Assuming an inter-individual 40% coefficient of variation in the population CL parameter estimate after weight-based allometric scaling, a sample size of 24 subjects would provide a margin of error of ± 16% in the 95% confidence interval of the CL estimate.

10.3 Analysis Plan

Population for Analysis
All subjects that receive at least 1 dose of study drug will be included in the safety analysis. All subjects with at least 1 evaluable PK sample will be included in the PK analysis n. If subjects have < 3 timed PK samples, additional subjects may be enrolled to ensure appropriate analysis.

Statistical Methodology
Descriptive statistics, such as number of observations, mean, median, 95% confidence interval, standard deviation, standard error, minimum, and maximum, will be presented by cohort for continuous variables (such as age, weight, and BMI). Other descriptive statistics, such as counts, proportions, and/or percentages, will be presented by cohort group to summarize discrete variables (such as race and sex).**Demographics and Baseline Characteristics**
The number of subjects completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be

summarized. Variables include race, ethnicity, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized by age and BMI cohorts.

Laboratory data, such as hematology and serum chemistry data, will be tabulated by age and BMI cohorts. Continuous laboratory measurements will be described using univariate 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.

Interim PK Analyses

An interim PK analysis of each age cohort will be performed after approximately 4 subjects have been enrolled into that cohort. If an interim analysis suggests that PK data is required on more than 12 subjects in that age cohort to evaluate the PK of clindamycin in this population, approximately 4 additional subjects will be enrolled into that age group for a total of 16 subjects.

PK Analysis

Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance. The influence of covariates (i.e., TBW, BMI, lean body weight, adjusted body weight, IBW etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each subject. The plasma concentrations-time profiles of clindamycin will be presented in figure form by subject and cohort (age and weight/BMI). Descriptive statistics will be presented for continuous and categorical variables. A detailed description of PK/PD analyses can be found in the PK analysis plan. We will compare PK parameters in this study of obese children to non-obese children.

11 SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in clinical trials. “Authorization” is required from each research subject (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the subjects' families. Consent forms describing in detail the study procedures and risks are given to the subject's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the subject's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject's legal guardian and answer any questions that may arise. The subject's legal guardian will sign and date the informed consent document prior to the subject being enrolled in the study. The subjects' legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects' legal guardians for their records. The rights and welfare of the subjects will be protected by emphasizing to their legal guardians that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the subjects' risk to receive the investigational product. This new information will be communicated by the investigator to subjects' legal guardians who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and subjects' legal guardians will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the subject consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed.

By signing the informed consent form, the subject's legal guardian agrees that the subject will complete all evaluations required by the trial, unless the subject is withdrawn voluntarily or is terminated from the trial for any reason.

12.1 Assent Process (e.g., Minor)

When a study includes subjects who may be enrolled in the study only with the consent of the subject's legally acceptable representative (e.g., minors), the subject should be informed about the study to the extent compatible with the subject's understanding. If capable, the subject should assent and sign and personally date the IRB-approved written assent form (if applicable based on local IRB guidelines). The assent form describes (in simplified terms) the details of the study, study procedures, and risks. Assent forms do not substitute for the consent form signed by the subject's legally acceptable representative. Consult with the institution's policies regarding enrollment of subjects who are unable to provide informed consent for themselves.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record subject data. The CRF will be used for the recording of all historical subject information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator. Data collection forms will be derived from the CRFs and provided by the DCC.

According to ICH E6, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file (regulatory binder) at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- MOP (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives,

microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the Principal Investigator, Pediatric Trials Network, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 50, 45 CFR 46 and 21 CFR 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

15.2 Institutional Review Board

This protocol is to be reviewed in accordance with subpart D of 45 CFR 46. Prior to its implementation, this protocol, including any subsequent amendments, the informed consent form, assent form, and any materials or advertisements presented to subjects, must be approved by an IRB constituted according to FDA regulations 21 CFR 56.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's federal-wide assurance number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Informed Consent

The investigator will choose subjects in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, a subject's parent/legal guardian will sign one informed consent for study enrollment. All subjects' parents/legal guardians must sign an informed consent form that complies with the requirements of both 21 CFR 50 and HIPAA before the subject enters the trial. A consent form that complies with the requirements of 21 CFR 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the subject's protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see **Section 12**.

15.4 Subject Confidentiality

Subjects will be assigned unique code numbers and will not be identified by name. Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. Clinical study sites will permit access to such records.

15.5 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments for 3 days following the last dose of study drug, unless there is an ongoing SAE for which the subject will be followed for up to 10 days after the last dose of study drug.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the CRFs and provided by the DCC to the sites to record and maintain data for each subject enrolled in the study that is not otherwise captured in the medical record. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the CRF should be consistent with the source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the source documents and CRFs.

16.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team in real time. The site data entry staff will ensure that they are accurate and complete, and will enter the data into AdvantageEDC^{SM} within 72 business hours of data acquisition. Serious adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee in real time, and entered into AdvantageEDC^{SM} within 24 hours of identification. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

16.2 Data Capture Methods

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

16.3 Types of Data

Data for this study will include demographic data, medical history, physical examination data including height/weight/BMI, safety, laboratory, and outcome measures including PK data.

16.4 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected quarterly.

16.5 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the Investigator for 10 years after the end of the study or per local/state regulations or until subjects reach 21 years of age, whichever is longer. Study information in a subject's medical records will be retained forever. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the PI when documents are no longer required to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the DCC's AdvantageEDC^{SM}.

A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB per their guidelines. The site principal investigator/study staff are responsible for knowing and adhering to their IRB requirements.

16.7 Subject Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in clinical trials. Authorization is required from each research subject (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 PUBLICATION POLICY

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

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

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research.

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APPENDIX I

CDC Male and Female Child BMI Percentile Charts

APPENDIX II

A. PROHIBITED DRUGS for ALL subjects:

1) CYP 3A4 potent inhibitors including:
   a. Cyclosporine
   b. Erythromycin, clarithromycin
   c. Itraconazole, ketoconazole
   d. Ritonavir, delavirdine, protease inhibitors
   e. Nefazodone, fluoxetine, gluvoxamine
   f. Verapamil and diltiazem
2) CYP 3A4 inducers
   a. Rifampin,
   b. Phenytoin
   c. Ritonavir
3) Other: St. John's Wart

B. PROHIBITED DRUGS (unless the subject was receiving these drugs prior to enrollment and was receiving clindamycin as part of routine care prior to enrollment):

1) Neuromuscular blocking agents: Clindamycin may enhance neuromuscular blocking effect.
   a. Atracurium
   b. Cisatracurium
   c. Pancuronium
   d. Rocuronium
   e. Succinylcholine
   f. Vecuronium

APPENDIX III

Capsule Dosing Tables

WT_Low	WT_High		mg/kg/day_low	mg/kg/day_high	Goal	Total Daily Dose
20	20	150/150/150/150	30.0	30.0	30 mg/kg/day	600
21	30	300/300/300	30.0	42.9	30 mg/kg/day	900
31	40	300/300/300/300	30.0	38.7	30 mg/kg/day	1200
41	45	450/450/450	30.0	32.9	30 mg/kg/day	1350
46	60	450/450/450/450	30.0	39.1	30 mg/kg/day	1800
61	72	750/750/750	31.3	36.9	30 mg/kg/day	2250
73	80	600/600/600/600	30.0	32.9	30 mg/kg/day	2400
	>81	900/900/900				2700
20	25	300/300/300	36.0	45.0	40 mg/kg/day	900
26	32	300/300/300/300	37.5	46.2	40 mg/kg/day	1200
33	38	450/450/450	35.5	40.9	40 mg/kg/day	1350
39	48	450/450/450/450	37.5	46.2	40 mg/kg/day	1800
49	56	750/750/750	40.2	45.9	40 mg/kg/day	2250
57	64	600/600/600/600	37.5	42.1	40 mg/kg/day	2400
	>64	900/900/900				2700

APPENDIX IV

Clindamycin in Non-Obese Children

Ref	*PO clindamycin:*			*Dose 1*		*Dose 13*	*Dose 17*		
	Dose Amount	Age range (years)	*No. Subjects*	C_{max} (1 hour) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{max} (1 hour) (mcg/mL)	Half-life (h)	AUC (mcg/mL * h)
14	2 mg/kg	7-12	11	1.24 (0.70)	0.19 (0.27)	0.72 (0.21)	2.46 (0.68)	1.51 (0.74)	4.64 (2.11)
14	3 mg/kg	6-12	11	2.25 (0.53)	0.44 (0.19)	1.23 (0.31)	2.98 (0.93)	1.98 (0.60)	9.28 (2.71)
14	4 mg/kg	8-14	10	2.44 (0.65)	0.51 (0.25)	1.45 (0.36)	3.79 (0.61)	2.22 (0.78)	9.35 (3.23)
14	2 mg/kg	3-7	13	1.22 (0.51)	0.18 (0.23)	0.55 (0.17)	2.21 (0.51)	-	-
14	2 mg/kg	0.5-2	8	1.22 (1.14)	0.30 (0.37)	0.60 (0.32)	2.53 (0.86)	-	-
	IV clindamycin:			*Dose 1*					
				C_{max}	Half-life (h)				
5	5-7mg/kg	"Pediatric Patients"		10	2.5				

* all values are means (standard deviation)
C_{max} – maximum concentration
C_{min} – minimum concentration
AUC – area under the concentration time curve

Pediatric Trials Network

Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLIN01

Phase I Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding Mechanism: Task Order

Protocol Number:	NICHD—2012-CLIN01
Protocol Date:	18JAN-2013
Protocol Version:	3.0
IND Number:	115396 (P. Brian Smith, IND holder)
Principal Investigator:	Michael J. Smith, M.D., M.S.C.E. Assistant Professor of Pediatrics University of Louisville Louisville, KY 40202 Telephone: Redacted Fax: Redacted E-mail: Redacted

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to, 45 CFR 46 (Human Subjects Protection, incorporating Subpart D: Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D: Additional Safeguards for Children in Clinical Investigations), and 21 CFR 56 (Institutional Review Board [IRB]).

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

SITE PRINCIPAL INVESTIGATOR STATEMENT

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

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

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

Redacted

Principal Investigator Name (Print)

Redacted

Principal Investigator Signature

7 OCTOBER 2013

Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

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

Redacted

Pediatric Trials Network Study

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Redacted

Principal Investigator Signature

7 OCTOBER 2013

Date

Table of Contents

SUPPLEMENTS/APPENDICES

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BPCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cl	Clearance
Cl/F	Oral apparent clearance
CMP	Comprehensive Metabolic Profile
CRF	Case Report Form
CYP	Cytochrome
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mg	Milligram
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*
N	Number (typically refers to subjects)
NIH	National Institutes of Health
PD	Pharmacodynamics
PG	Pharmacogenomic
PK	Pharmacokinetics
PO	Oral
SAE	Serious Adverse Event
t1/2	Half-life
TBW	Total Body Weight
Vd	Volume of Distribution

V/F	Oral apparent volume of distribution

Protocol Synopsis

Protocol Title:	Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLIN01
Phase:	I
Product:	Clindamycin phosphate (intravenous) Clindamycin hydrochloride (oral capsules) Clindamycin palmitate (oral solution)
Objectives:	Primary: Determine the pharmacokinetics (PK) of intravenous clindamycin in overweight and obese children and adolescents Secondary: 1) Determine the PK of oral clindamycin in overweight and obese children and adolescents 2) Characterize the safety profile of clindamycin in overweight and obese children and adolescents
Study Design:	Prospective, multi-center, open-label, multiple-dose PK study of intravenous and oral clindamycin
Study Population:	Children ages 2 – < 18 years of age with body mass index (BMI) ≥ 85 percentile for age
Number of Subjects:	24–32 evaluable subjects
Number of Sites:	Up to 6 sites
Duration of Subject Participation:	Up to 18 days (1-day screening period, minimum of 2 doses prior to PK samples and maximum of 14-day treatment period, and 3-day observation period after study drug administration to monitor for serious adverse events)
Dose Schedule:	30–40 mg/kg/day dosed every 6 or every 8 hours with a maximum daily dose of 2.7 grams/day. Dosing greater than 2.7g/day will be allowed for children receiving clindamycin as standard of care.
Estimated Start:	October 2012
Estimated Time to Complete Enrollment:	Approximately 24 months
Inclusion Criteria:	1) 2 years – < 18 years of age at the time of first dose of study drug 2) Suspected or confirmed infection OR receiving intravenous clindamycin per routine care 3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug 4) BMI ≥ 85th percentile for age and sex, based on CDC recommendations

	5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)
Exclusion Criteria:	1) The following apply only to those who are NOT already receiving clindamycin as part of routine care: a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin b. History of *C. difficile* colitis with previous administration of clindamycin c. Aspartate aminotransferase (AST) > 120 units/L d. Alanine aminotransferase (ALT) > 210 units/L e. Total bilirubin > 3 mg/dL f. Serum creatinine > 2 mg/dL g. Receiving a neuromuscular blocker as part of therapy (see **Appendix II**) 2) Previous participation in the study 3) Subject is on prohibited medication or herbal product (see **Appendix II**) 4) Subject is receiving extracorporeal life support (ECLS) 5) Subject is post-cardiac bypass (within 24 hours) 6) Subject on inotropes/pressors 7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

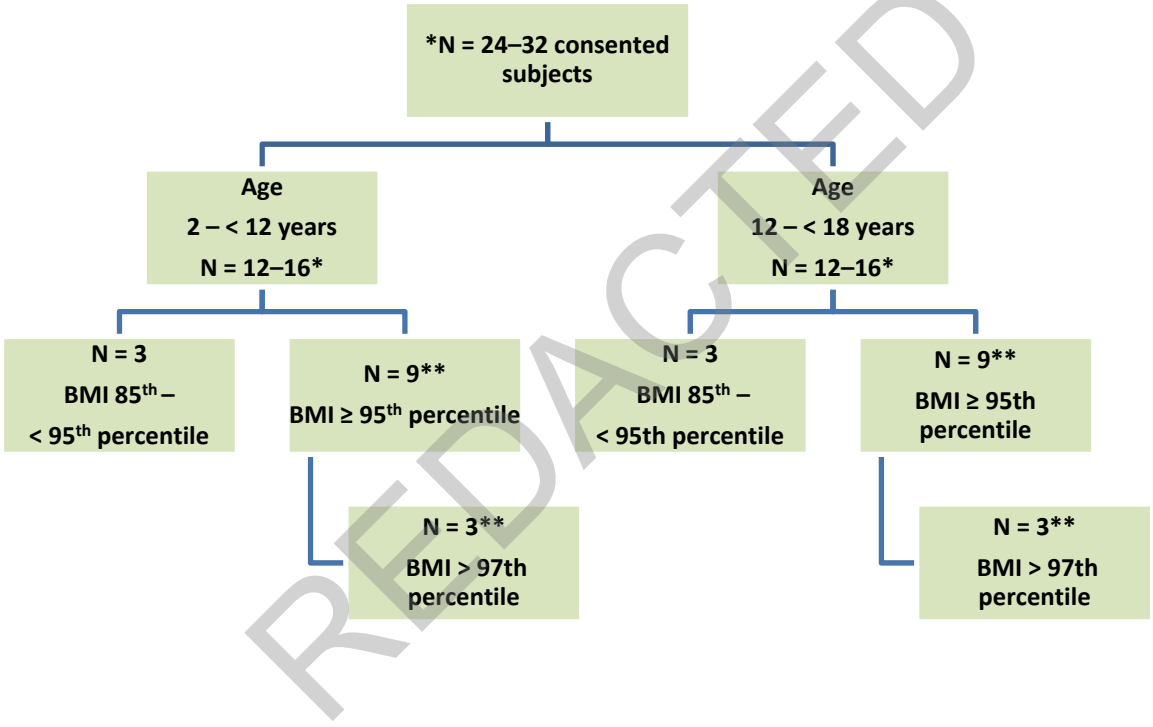
Table 1. Study Event Table

Study event/day	Screening/ study day 0	Study day 1 (any dose after the 1st dose of IV clindamycin; oral PK with 4th dose or later)	Study day 2–14	End of therapy OR early withdrawal or discontinuation	3-Day post-treatment phone follow-up
Informed consent/ assent & HIPAA	X				
Medical history	X				
Demographics	X				
Concomitant medications	X	X	X	X	X
Infection history	X	X			
Physical examination	X			X	
Weight	X				
Height	X				
BMI	X				
Waist:hip ratio	X				
Laboratory evaluation[a]	X			X	
α-1 glycoprotein (ELISA kit)[b]	X				
Laboratory evaluation (6.6.1 Table 2—if obtained as part of routine care)		X	X		X
Serum pregnancy test (female only)	X				
Feeding status (during PO PK portion only)		X			
Discarded scavenged samples[c]		X	X	X	
Clindamycin IV or PO[d]	X	X	X[f]		
PK samples[e]		X			
AE/SAE	X	X	X	X	X

[a]CBC, CMP.
[b]May be performed at any time during the study if not obtained at baseline.
[c]Discarded blood cells may be collected at any time during the study.
[d]Group assignment (see Figure 1).
[e]PK sampling (Table 3, see Section 6.6.2).

[f]IV clindamycin will be continued per treating physician; when switched to PO, subject will participate in PO PK study.

Figure 1. Schematic/Description of Study Design



*IV subjects who transition to oral clindamycin will participate in the oral PK study.
**Minimum of 3 subjects with BMI > 97th percentile in each age group.

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Over the past decade, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a leading cause of hospitalization for children and adolescents in the United States (1). Consequently, the use of antimicrobial agents active against MRSA has become more prevalent (2). Specifically, the use of clindamycin among children hospitalized with *Staphylococcus aureus* infections increased from 21% in 1999 to 63% in 2008. At the same time, rates of childhood obesity have continued to remain high. Recent national data demonstrate that 17% of children aged 2–19 years in the United States are obese (body mass index [BMI] ≥ 95th percentile) and 12.3% are morbidly obese (BMI ≥ 97th percentile) (3). Obese patients have a greater likelihood of complications from infectious diseases and are at increased risk of developing *Staphylococcus aureus* infections. Therefore, an understanding of the PK of clindamycin in this population is critical to ensure appropriate interventional therapy.

Clindamycin, a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin (4), is approved by the U.S. Food and Drug Administration for the treatment of pediatric and adult patients with respiratory tract, female pelvis and genital tract, and skin and soft tissue infections with susceptible bacteria including streptococci, pneumococci, and staphylococci. Clindamycin is also approved in adults for septicemia and intra-abdominal and serious infections with susceptible anaerobic bacteria (5).

Clindamycin is approximately 90% protein-bound. It is metabolized by the liver and excreted via the liver, bile, and kidneys. Impaired renal function modestly decreases the elimination of clindamycin; however, dosage adjustment is not required with renal dysfunction (4). Clindamycin phosphate (intravenous [IV] formulation) is rapidly converted to active clindamycin which has an elimination half-life of about 3 hours in adults and 2.5 hours in children (5). The drug penetrates well into all tissues, with the exception of the brain and cerebral spinal fluid. It is actively taken up and concentrated within the phagocytic cells. Clindamycin binds to the 50S subunit on the bacterial ribosome and inhibits protein synthesis by interfering with the formation of initiation complexes, thus inhibiting exotoxin production (4). Clindamycin exhibits time-dependent killing; and efficacy is correlated with the time clindamycin concentrations exceed the minimum inhibitory concentration of the pathogen of interest. A summary of clindamycin serum concentrations in non-obese children is found in Appendix IV.

Variability in serum and tissue concentrations has been reported in obese patients (4). The underlying premise is that this is due to physiologic changes that alter a drug's volume of distribution (Vd) and body clearance (Cl) (6,7). Thus, obese patients may be dosed inappropriately if fixed or "adult" doses are used (under-dosed) or if weight-based dosing is used (over-dosed) (6,7). Because critically ill obese patients with infections are reported to have a worse outcome than non-obese patients (8), it is imperative to determine if the disposition of and response to clindamycin may be altered compared to healthy children with an infection. In addition, sub-therapeutic drug concentrations may increase the development of resistant organisms. Thus, it is important to perform pharmacokinetic (PK) and pharmacodynamic (PD)

studies in the obese pediatric population to ensure that these patients are being optimally dosed with medications designed to treat infections. There are no currently available PK (or PD) data to guide clindamycin dosing in obese pediatric or adult patients. This proposal will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years.

2.2 Scientific Rationale

Selection of the correct drug dose and dose regimen is the most important decision in ensuring optimal pharmacotherapy. Defining an optimal regimen requires a clear understanding of the drug's PK, PD, and, for many compounds, pharmacogenomic (PG) profiles. Understanding these characteristics for drugs used in pediatrics is imperative to determine optimal dose regimens across the pediatric age continuum.

Clinically, drug dosing in pediatrics is individualized to age by basing the drug dose on a patient's body weight and the dose interval on the functional capacity of the drug's clearance pathways. This approach assumes, though inaccurately, that a drug's Vd and body Cl are directly proportional to a patient's body weight. Despite this lack of proportionality, the majority of pediatric patients favorably respond to weight-based drug dosing. However, as the potency of newer drugs increases and the need for more precise drug dose regimens expands, better-defined dose regimens based on careful assessment of the drugs' integrated PK-PD-PG profiles across the pediatric age continuum are needed (9). Complicating this paradigm are the substantially increasing numbers of children and adolescents who are obese, and even morbidly obese, and the lack of data on disposition in the obese population. Clinical trials of new drugs focused on FDA labeling exclude obese patients, leaving the determination of dosing regimens in the obese for post-marketing, often investigator-initiated studies.

Antibiotic Dosing Regimens Based on PK-PD Modeling
Prior to our understanding of the integrated PK-PD characteristics for antibiotic drugs, antibiotic dosing regimens were mostly based on perceived maximum tolerated doses often related in some manner to the target pathogen minimum inhibitory concentration (MIC). Integration of an antibiotic's PK with PD allows for the determination of the optimal dose regimen across the spectrum of antibiotic drugs (10,11). In addition, this more quantitative approach permits comparisons of different antibiotic drugs for a specific infection and far more accurate predictability of patient response. The specific antibiotic PK-PD characteristic used to predict outcome (i.e., bacteriologic eradication) appears to be mostly dependent on whether the drug's bacterial killing is concentration- or time-dependent. Clindamycin is most often described as a "time-dependent antibiotic with moderate persistent effects," and as such, the best predictor of bacterial killing appears to be the ratio of the area under the clindamycin (free, unbound) drug concentration time curve (AUC) divided by the targeted pathogen MIC (i.e., fAUC/MIC) (11). To accurately determine this pivotal PK-PD parameter, what is needed is a comprehensive understanding of the drug's PK profile across the age spectrum while incorporating the spectrum of pathophysiologic changes and differing body habitus. For clindamycin, these data are not available.

Clindamycin Pharmacokinetics
Limited published clindamycin PK data exist and encompass < 100 neonates, infants, and children. In neonates, clindamycin elimination is delayed compared with older infants and children—mean elimination half-life (t ½) values of 8.7 vs. 3.6 hours, respectively (12,13).

Regardless of age group studied, variability was observed in clindamycin t ½, Vd, AND systemic Cl. In addition, some studies report variable serum clindamycin concentrations (bioactivity) following parenteral dosing (12,14). Despite this variation in drug disposition, which is observed in both children and adults, bioactive serum clindamycin concentrations remain therapeutic following routine parenteral (intramuscular [IM], IV) or oral dosing. Considering that clindamycin, an antibiotic, is used to treat infections caused by susceptible pathogens responsible for infectious diseases regardless of patient age, pediatric clindamycin development strategies need only focus on the drug's safety and PK profile to ensure similar systemic exposure. Available clindamycin PK data support close similarity for clindamycin systemic exposure (i.e., bioactive serum clindamycin concentrations and AUC) in older infants, children, and adults following comparable mg/kg doses (12, 14-191). As noted above, clindamycin PK in premature and full-term infants is, as expected, different than that observed in older patients (12,13). This foundation of data underscores the importance of studying clindamycin disposition in the obese pediatric patient.

Clindamycin is extensively bound to plasma protein, primarily to alpha 1 acid glycoprotein, and, with the exception of the brain or cerebrospinal fluid, effectively penetrates body tissues and fluids. The drug is metabolized primarily by the cytochrome (CYP) P450 isoenzyme CYP3A4 to two primary, antimicrobial active metabolites, a sulfoxide and to a lesser extent N-demethylclindamycin (20). Although only limited data are available for current clindamycin pediatric dosing regimens, the regimens employed clinically have been used for decades with apparent success. Nevertheless, clindamycin optimal dosing regimens in pediatrics remain unknown. Furthermore, the influence of obesity on clindamycin disposition is unknown and may have a far greater negative impact on patient outcome due to ill-defined, clinically extrapolated dosing.

Drug Dosing and Obesity

Data defining optimal drug dosing in the obese and morbidly obese adult patient are very limited and virtually non-existent in pediatrics. Drug dosing on total body weight (TBW) in the obese patient has the real risk of overdosing the patient, resulting in an increased incidence of adverse effects, while dosing on ideal body weight (IBW) can lead to serious under-dosing. In obese adults, IBW is increased by 20–40%, which is unaccounted for when using the many mathematical formulas available to calculate dosing based on a person's IBW. This deficiency may partially explain the inaccuracy of drug dose regimens for obese patients based on IBW formula estimations (21–26).

The influence varying degrees of obesity have on important physiologic functions across the age continuum in pediatrics is unknown. In adults, sparse data suggest that obese adults may have altered tissue blood flow rates due to inherent differences in blood flow to lean (greatest amount) and adipose tissue, impaired cardiac function, and alterations in phase I and II metabolism. Although intuitive, one might assume that a drug's Vd would be increased in obese patients for lipophilic compounds, though in fact, for the few drugs assessed, the Vd is highly variable. Similarly, Cl is also highly variable in the obese population, underscoring the need to determine drug disposition characteristics not only across the age continuum but also with increasing degrees of obesity (21–24). No such data are available for the pediatric patient, but these data combined underscore the need to critically assess a drug's disposition relative to age and body habitus. Furthermore, for antibiotics whose efficacy is dependent on achieving effective concentrations at the infectious site, interfaced with the organism, optimal dosing in the obese pediatric patient must be defined (6,7).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of Blood Draws
There are small risks to blood sampling, usually some pain/discomfort with the blood stick. Every effort will be made to avoid additional (to standard of care) sticks for this study by timing clinical blood draws to coincide with timed samples when possible and the use of existing IV lines when feasible for the blood draws.

Risks of Clindamycin
From the FDA label and review of the literature, the following are adverse reactions of clindamycin: antibiotic-associated colitis, pseudomembranous colitis, abdominal pain, nausea, and vomiting; hypersensitivity reactions (maculopapular rash and urticaria have been observed during drug therapy; generalized mild-to-moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions; rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin; a few cases of anaphylactoid reactions have been reported). Organ systems that are affected include skin and mucous membranes (pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported); liver (jaundice and abnormalities in liver function tests have been observed during clindamycin therapy); renal system (although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances); hematopoietic (transient neutropenia [leukopenia] and eosinophilia have been reported; reports of agranulocytosis and thrombocytopenia have been made; no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances); local reactions (pain, induration, and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion); musculoskeletal (rare instances of polyarthritis have been reported); cardiovascular (rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV administration). There is minimal additional risk to the subjects who are receiving clindamycin as part of their routine medical care.

2.3.2 Known Potential Benefits

The subject may benefit from the use of the study drug; however, participation in this study has no other potential benefits to the subjects. The results of this study may benefit overweight and obese subjects in the future who require clindamycin therapy.

3 OBJECTIVES

Primary Aim
Characterize the PK of multiple-dose IV clindamycin in overweight and obese children and adolescents.

Secondary Aims
1. Characterize the PK of multiple-dose oral clindamycin in overweight and obese children and adolescents.
2. Characterize the safety profile of clindamycin in overweight and obese children and adolescents.

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1. PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUCtau)

3.1.2 Secondary Outcome Measures

1. PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2. Safety profile: Adverse events will be collected during and after study drug administration..

4 STUDY DESIGN

This will be a prospective, open-label PK and safety profile study of multiple doses of IV and oral clindamycin in overweight and obese children 2 – < 18 years of age. The total study duration is expected to be approximately 24 months; each subject will participate in the study for up to 18 days (screening day; treatment days 1–14 [may be as short as 2 days] followed by an observation period of 3 days post discontinuation of clindamycin therapy or after day 17 (on day 18) of therapy in those who are treated with more than 14 days of clindamycin).

5 Study Population

Selection of the Study Population

Eligible subjects ages 2 – < 18 years will be identified through the inpatient units at each participating site. There will be up to 32 evaluable subjects (defined in Section 10.3) enrolled; however, target enrollment will be 24 subjects. If dosing changes are suggested by the interim PK analysis (see **Section 10.3**), approximately 8 additional subjects will be enrolled. Twelve to 16 subjects will be enrolled in each of the following age groups: 2 – < 12 years and 12 – < 18 years of age. Subjects will be further stratified into 1 of 2 groups based on their BMI (85^{th} – < 95th percentile, and ≥ 95th percentile). No more than 3 subjects with BMI in the 85^{th} – < 95th percentile will be enrolled in each age group. Participating sites will prioritize enrollment of subjects with BMI > 97^{th} percentile in each age group.

5.1 Inclusion/Exclusion Criteria

The investigator or other study site personnel will document in the source documents (e.g., the hospital chart) that informed consent and assent (if applicable) were obtained. Laboratory tests or non-pharmacologic treatment procedures that were performed and considered "routine care" within 72 hours of first dose of study drug may be used for screening procedures required by the protocol and recorded in the case report form (CRF).

Inclusion Criteria

1) 2 years – < 18 years of age at the time of first dose of study drug
2) Suspected or confirmed infection OR receiving IV clindamycin per routine care
3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug
4) BMI ≥ 85^{th} percentile for age and sex, based on CDC recommendations
5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

Exclusion Criteria

1) The following apply only to those who are NOT already receiving clindamycin per routine care:
   a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin
   b. History of *C. difficile* colitis with previous administration of clindamycin
   c. AST > 120 units/L
   d. ALT > 210 units/L
   e. Total bilirubin > 3 mg/dL
   f. Serum creatinine > 2 mg/dL
   g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II**)
2) Previous participation in the study
3) Subject is on prohibited medication or herbal product (see **Appendix II**)
4) Subject is receiving extracorporeal life support (ECLS)

5) Subject is post-cardiac bypass (within 24 hours)
6) Subject on inotropes/pressors
7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

5.2 Treatment Assignment Procedures

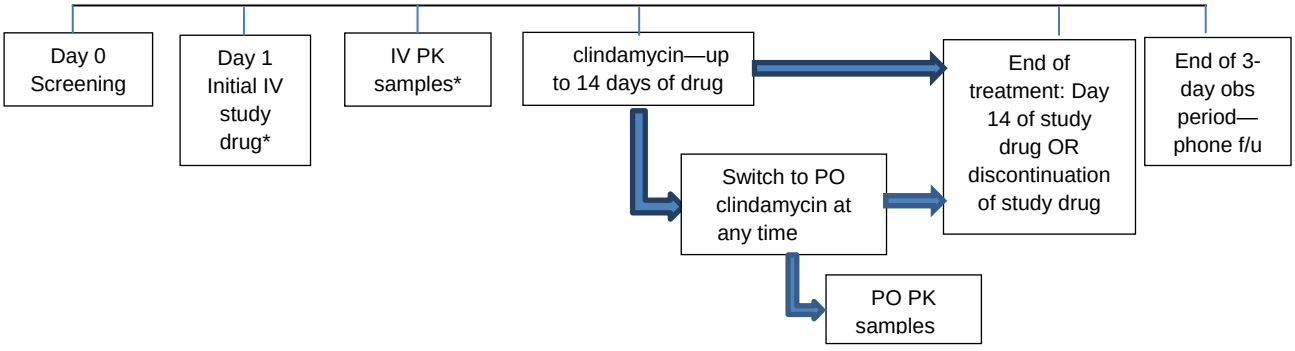
This will be an open-label PK study. Subjects will be assigned to age groups based on age upon first dose of study drug and to a BMI group based on BMI at study entry.

5.2.1 Duration of Study Participation

Duration of therapy will be up to 14 days for children who receive the first dose of clindamycin as the study drug. All subjects will begin on IV therapy and must receive at least 2 doses of IV clindamycin to participate in the study. The total duration of therapy with clindamycin will be determined by the treating physician for those children who are receiving clindamycin as part of routine care; however, only 14 days of therapy from the time of enrollment will be considered as study drug. If therapy extends beyond 14 days, the study follow-up visit/call will occur on day 18 (after completion of 3 safety observational days [72–96 hours]). Patients who are receiving antimicrobial agents other than clindamycin may enroll in this study and receive up to 3 doses of IV clindamycin and 4 doses of oral clindamycin in addition to their standard of care therapy. Subjects who transition to oral clindamycin may return as outpatients to complete the PK portion of the study.

Total duration of study participation will be up to 18 days. This will comprise a 1-day screening period; a minimum 2 doses of IV and 4 doses of oral clindamycin before PK sampling begins for IV and oral routes, respectively; a maximum 14-day treatment period; and a 3-day post-study observation period to monitor for serious adverse events. The 3-day post-treatment visit may be a phone follow-up. Patients may continue clindamycin per their physician's recommendation after they have completed participation in this (maximum of) 18-day study.

Figure 2.Timeline



*Minimum of 2 doses of IV clindamycin before IV PK period.

**Minimum of 4 doses of PO clindamycin before PO PK period.

5.2.2 Replacement Subjects

Subjects in the IV portion of this study who are unable to provide at least 3 timed PK samples may be replaced.

5.2.3 Reasons for Subject Withdrawal

A subject or his/her parent/guardian may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time. Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject or investigator noncompliance with the study protocol
- At the request of the subject, investigator, treating physician, or sponsor
- Adverse reaction or suspected adverse reaction.

Subjects are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. The subject who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations, and will be provided appropriate care under medical supervision until the symptoms of any adverse event (AE) resolve or the subject's condition becomes stable. Subjects withdrawn from the study due to an AE must be followed per protocol (see **Section 8.2.4**).

5.2.4 Termination of Study

This study may be terminated at any time by NICHD, the Investigational New Drug Application (IND) sponsor, or the Data Monitoring Committee (DMC) if serious adverse reactions occur in 2 or more subjects that are directly related to study drug, or if, in NICHD's judgment, there are no further benefits to be achieved from the study. A study site may be terminated if the investigator does not adhere to the study protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

See the schedule of study events and procedures on page xi (**Table 1**).

1. Medical history will be obtained by interview with the parent/legal guardian/subject and from the subject's medical records.

2. Concomitant medications of interest administered within 72 hours prior to and during the period of administration of study drug, including herbal products of interest, will be recorded (see **Appendix II**).

3. Physical examination, including abnormal physical findings, height (measured standing if possible), weight and waist:hip ratio will be obtained. BMI will be calculated from height and weight using the following formula: BMI = [weight (kg) / (stature (cm))^2] x 10,000. Please refer to the website for the Centers for Disease Control (CDC) pediatric BMI calculator (http://apps.nccd.cdc.gov/dnpabmi/). The BMI percentile will be obtained using the BMI calculator and verified using the age- and sex-specific CDC BMI charts (**Appendix I**).

4. The safety laboratory testing complete metabolic panel (CMP) and complete blood count (CBC) will be performed at each site's local laboratory. Baseline CMP and CBC may be used if obtained as part of routine care within 72 hours prior to study enrollment. The serum pregnancy test will also be performed at the local laboratory (within 24 hours prior to study enrollment). Alpha-1-glycoprotein will be measured using an ELISA kit (central laboratory) at one time point after consent.

5. PK samples will be obtained with the second or subsequent doses of clindamycin for IV PK samples and after 4 doses of oral clindamycin (see **Section 6.6.2**).

6.2 Screening

Research staff at sites will screen potential subjects for eligibility requirements. A Waiver of Informed Consent and HIPAA Authorization will be included in each site IRB application for the purpose of ascertainment (identification, selection) and/or recruitment of potential subjects while recording identifiable private information, such as protected health information (PHI), prior to obtaining the subject's consent. IRB approval of the waiver will be in accord with the criteria for a waiver of consent and HIPAA authorization as applied to the limited portion of study activity to which the waiver will apply: prescreening, contact and recruitment procedures as described in the protocol and IRB application. Informed consent form must be signed before any protocol-specific procedures are performed to determine eligibility.

6.3 Enrollment/Baseline

Baseline/Pre-Dose Assessment (Day 0)
After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA documents, the subject has signed assent (if applicable), and after it has been determined that the subject satisfies all inclusion and no exclusion criteria, the following evaluations will be performed and recorded in the CRF:

1. Subject demographics
2. Physical examination, including weight, height, waist:hip ratio and BMI
3. Pertinent medical history
4. Concomitant medications (72 hours prior to first dose of study drug)
5. Laboratory determinations (see **Table 2, Section 6.6.1**)
6. Culture results of blood, urine, sputum, or wound (if obtained as part of routine care) within 72 hours prior to the first dose of study drug
7. For subjects receiving clindamycin per routine care, the date and time for the doses administered prior to first dose of study drug will be recorded (up to a maximum of 6 prior doses)
8. Serum pregnancy test (females only who have reached menarche) within 24 hours of study enrollment

Assessments/Procedures (Days 1–14)
The subject will start study drug upon completion of the pre-assessment, or, if s/he was already receiving clindamycin (at the study-recommended dose), s/he will continue receiving that dose of clindamycin. If s/he was receiving clindamycin at a dose lower than the study-recommended dose, the dose will be changed to be in compliance with the protocol. Total body weight will be used to calculate the absolute dose administered. Refer to **Section 7.1.2** for dosing. Subjects who transition to oral therapy will participate in the oral-dose PK portion..

The following assessments will be conducted after the subject receives the first dose of clindamycin after study enrollment and throughout therapy up to day 14:

1. Concomitant medications of interest (see **Appendix II**)
2. Start date/time and stop date/time of clindamycin administration and flush date/stop time after IV administration
3. Feeding status (during PO PK portion only): NPO, clear liquids, full feeds, etc.
4. Collection of PK samples (including date/time); see **Section 6.6.2**
5. Laboratory results for laboratory tests of interests (see **Section 6.6.1**)
6. Collection of culture results (if available)
7. Adverse events (see **Section 8.2.1**)

6.4 End of Therapy OR Early Withdrawal/Discontinuation

The following assessments will be conducted at early withdrawal or end of therapy:

1. Concomitant medications of interest (see **Appendix II**)

2. Physical examination
3. Laboratory evaluations (see **Section 6.6.1**)
4. Adverse events (see **Section 8.2.1**)

6.5 Follow-up Safety Phone Call

Assessments/Procedures (Day 3 Post Treatment): This visit will be a phone follow-up unless the subject is still hospitalized. This assessment must occur at least 72 hours but no more than 96 hours after the last dose of study drug. The following information will be obtained:

1. Adverse events (see **Section 8.2.1**)
2. Concomitant medications
3. Any labs collected

6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

The safety laboratory testing (CMP and CBC) will be performed in the local laboratory at each site. CMP and CBC performed as part of routine care within 72 hours prior to enrollment may be used for baseline laboratory tests. A CBC and CMP will be obtained at the end of therapy (any hematology or chemistry values obtained within ± 24 hours of discontinuation of study drug or within ± 24 hours of completion of 14 days of study drug (if they are continuing clindamycin beyond 14 days) may be used as end-of-treatment laboratory values). If these laboratory tests have not been performed as part of routine care, they will be performed for the study per the protocol schedule. The serum pregnancy test will also be performed at the local laboratory. Alpha (α)-1-glycoprotein will be performed once during the study using an ELISA kit (central laboratory).

Table 2. Laboratory Evaluations

Hematology	Serum Biochemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Platelets	Chloride
White blood cells	Bicarbonate
	Total calcium
	Glucose
	Creatinine
	Blood urea nitrogen
	Total protein
	Albumin
	Aspartate aminotransferase
	Alanine aminotransferase
	Bilirubin
	α-1 glycoprotein (central laboratory)

6.6.2 Special Assays or Procedures

PK Samples
Blood (0.5 mL) will be collected with scheduled IV and oral doses of clindamycin for clindamycin plasma concentration determinations (see **Table 3** below for schedule). In subjects receiving IV clindamycin, PK samples should be collected from a site separate from the site of administration. PK samples in subjects on IV clindamycin will be collected with any dose after the first dose of study drug (excluding the first dose), and, for PO clindamycin, PK samples will be collected with the fourth dose or any dose after the fourth dose. The PK sampling will be drawn according to the following schedule relative to the end of infusion (IV PK) or actual time of oral administration (PO PK).

Table 3. PK Schedule

Scheduled PK Sampling Times				
Time (hours)*	**IV dose***		**PO dose**	
	Q6h	**Q8h**	**Q6h**	**Q8h**
Pre-dose 0 (within 15 minutes prior to the dose)	**X****	**X****	**X****	**X****
0.5 (± 5 minutes)	**X****	**X****	N/A	N/A
1–1.5	X	X	**X****	X**
3–4	**X****	**X****	**X****	--
5–6	--	X	--	**X****
Pre-dose (will depend if on q6h or q8h dose schedule)	**X****	**X****	**X****	**X****
Total number of samples	5	6	4	4

* Time starts at end of flush after the 30-minute infusion.
** Priority samples (see paragraph below).

Every effort should be made to collect all PK samples for each subject. Collection of PK samples should be timed with collection of laboratory tests per standard of care to minimize blood draws specifically for the study. If it is impractical to collect all PK samples during the same dosing interval, samples can be obtained at different dosing intervals. If it is impossible to obtain all PK samples for each subject, **PK samples can be prioritized to include:**

a) **For IV administration: pre-dose, 0.5 hours, 3–4 hours, and pre-next dose**
b) **For oral administration: pre-dose, 1–1.5 hours, 3–4 hours (q6h dosing), 5–6 hours (q8h dosing), and pre-next dose**

Clindamycin concentrations in plasma will be measured at a central laboratory using a validated bioanalytical assay. In addition, scavenged samples will be obtained.

Scavenged Plasma Sampling
Plasma samples collected in EDTA tubes during the course of therapy (~100 µL plasma or ~200 µL whole blood) will be procured, after consent. A maximum of 10 scavenged plasma samples will be collected per subject. Collection may begin with any specimen collected after the first dose of study drug through 24 hours after the last dose of study drug. The date and time of

sample collection, as well as the date and time the sample is frozen, will be collected for all scavenged samples.

Minimizing Blood Loss
To minimize the amount of blood sampling, hematology and chemistry laboratory measures will be obtained only at baseline and end of study. If they have been obtained as part of routine care within 3 days prior to enrollment into the study, the baseline CMP and CBC do not need to be repeated. The PK sampling scheme will be employed such that no more than a total of 8 mL (< 3 mL/kg) of blood is obtained from each subject for PK analysis. Plasma samples will be collected in 0.5 mL blood aliquots.

6.6.3 Specimen Preparation, Handling, Storage, and Shipping

Detailed information for collection, labeling, preparation, handling, storage, and shipping of specimens is detailed in the manual of procedures (MOP).

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

A dose of 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 g/day is selected based on current labeling. Patients who are receiving clindamycin as part of their routine care are also eligible to participate if their dose can be adjusted to be at least 30 mg/kg/day upon enrollment. The dose administered will be based on TBW. Because bioavailability is estimated at 85%, the same dose will be used for oral administration as is used for IV dosing. Both solution and capsule preparations will be included in this study because both oral formulations are utilized in clinical practice, and it will allow the inclusion of those patients who cannot swallow pills. In the absence of PK data, we assume that drug clearance will be comparable in obese pediatric patients compared to non-obese pediatric patients. Therefore, a dosing regimen 30–40 mg/kg per day and a maximum dose of 2.7 g/day should provide exposures similar to those used in children and adolescents with a normal BMI. It is predicted to be safe in the obese population because similar doses are currently used per routine care.

7.1.2 Dose and Timing

Both q6h and q8h dosing will be allowed for both oral and IV dosing of clindamycin. For children receiving clindamycin as part of clinical care, this protocol will not prescribe a route of administration or dosing interval; the dose, route of administration, and dosing interval prescribed by the treating physician will be recorded on the CRF. Dosing greater than 2.7g/day will be allowed for children receiving clindamycin as part of clinical care. However, if the prescribed dose is less than the lowest dose for this study, the dose of clindamycin will be changed to comply with the study-recommended dose. See **Section 5.2.1** for duration of therapy.

IV dosing: A minimum of 2 doses of IV clindamycin will be administered. The dose administered will be based on TBW at 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 grams/day. The drug will be administered over 30 minutes. The venous access line will be flushed per local practice of the completion of IV administration, and the time of the end of flush will be documented.

Oral dosing: For those subjects who are receiving clindamycin as a solution, they will receive 30–40 mg/kg/day divided q6h or q8h. For those subjects receiving the capsule formulation, they will receive the dose of clindamycin defined in **Appendix III**. Only whole capsules will be used. The oral solution will be used for those subjects who cannot swallow capsules. During the PO phase of the study, PK samples should be obtained with the fourth dose of PO clindamycin (but may be collected with a later dose if unable to do the fourth dose). No more than 12 PO study drug doses will be administered as part of this study.

7.1.3 Formulation, Packaging, and Labeling

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules.

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles for reconstitution.

Each formulation is approved for use in the United States.

7.1.4 Product Storage and Stability

Clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules), and clindamycin palmitate (PO oral solution) will all be stored at room temperature (20–25^0 C). Diluted clindamycin phosphate (IV) is stable at room temperature for at least 16 days and refrigerated for at least 32 days. Reconstituted clindamycin palmitate hydrochloride, USP for oral solution is stable for 2 weeks at room temperature and should not be refrigerated. See the MOP for detailed information.

7.2 Preparation and Administration of Study Intervention/Study Drug

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL. The drug will be infused over 30 minutes. Infusion rates should not exceed 30 mg/minute. The pharmacy will prepare the IV formulation, and the dose administered will be based on TBW.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules, and the dose will be dispensed based on TBW (see **Appendix III** for dosing).

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles and will be prepared in the pharmacy at each site based on the reconstitution recommendation in the label. The dose administered will be based on TBW.

Refer to the MOP for additional details regarding drug procurement, drug preparation, and administration.

7.3 Modification of Study Intervention/Investigational Product for a Subject

No dosing adjustments are required for hepatic or renal impairment.

7.4 Accountability Procedures for the Study Intervention/Study Drugs

Each site will provide drug for their study subjects. The study product accountability records will be maintained in the pharmacy study binder for clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules) and clindamycin palmitate (PO oral solution). See MOP for specific details related to investigational product accountability.

7.5 Assessment of Subject Compliance w/ Study Intervention

Compliance with dosing will be determined using the pharmacy accountability logs and the subject's medication administration record. For those subjects who are discharged on oral clindamycin and have not completed the PO PK visit, the subject will keep a drug administration diary and all drugs will be accounted for at the outpatient PK study visit.

7.6 Concomitant Medications/Treatments

Prohibited drugs are listed in **Appendix II**.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

AEs will be collected during and after study drug administration and for 3 days following end of therapy with clindamycin. Results will be tabulated by MedDRA System Organ Class and Preferred Term.

8.2 Methods & Timing for Assessing, Recording, & Analyzing Safety Parameters

AEs will be collected from the time of consent, throughout the period of study drug administration, and for 3 days following end of therapy with clindamycin. See **Section 8.6** for clarification for AEs identified at the 3-day follow-up visit and for serious AEs (SAEs). Safety will be assessed by frequency and incidence of AEs and SAEs. The Best Pharmaceuticals for Children Act (BPCA) safety monitoring committee (DMC) convened by NICHD will review data and safety information from study subjects.

8.2.1 Adverse Event

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

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

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

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

1. Death
2. Life-threatening AE (“life-threatening” means that the study subject was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.2.2 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, investigational plan, or informed consent.

8.2.3 Identification of Events and Timeframe for Reporting

As all subjects in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after consent has been obtained. The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome. Any event beginning more than 3 days after the last dose of study drug will not be captured.

8.2.4 Follow-up of Adverse Events

AEs ongoing at the time of the last dose of study drug will be followed up to 3 days after the last dose of study drug. AEs that resolve during the study or follow-up period will have the resolution date documented in the CRF. Adverse events that are identified at the last assessment visit/phone contact (or at the early termination visit) must be recorded on the AE CRF, with the status of the AE noted. Any events that are identified at the last assessment visit/phone contact will be followed for an additional 3 days for AEs and 10 days for SAEs and if still ongoing can be "resolved by convention". All serious suspected adverse reactions will be followed until resolution. All enrolled subjects in both cohorts who receive at least 1 dose of clindamycin will be followed for safety.

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Subject is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. **MODERATE**: Subject experiences enough symptoms or findings to require intervention

3. **SEVERE**: Subject experiences symptoms or findings that require significant intervention

8.4 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction. ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.5 Reporting Procedures and Timeframe for Reporting

All AEs will be entered into the data system within 72 business hours of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties encountered when entering the event into the electronic data capture (EDC) system, the SAE will be reported to the data coordinating center (DCC) by telephone or FAX communication. Investigators must submit safety reports as required by their local IRB, independent of the reporting requirements specified in the protocol.

8.5.1 Serious Adverse Events

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC, IND sponsor, and funding sponsor (NICHD). The BPCA DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.5.2 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The sponsor or his representative will submit expedited safety reports (IND safety reports) to the FDA and other regulatory agencies as necessary, and will inform the DMC and investigators of such regulatory reports. Site investigators must submit IND safety reports as required by their IRB. Documentation of the submission to and receipt by the IRB should be retained for each IND safety report. The sponsor will submit a progress report of the investigation annually, which will include a summary showing the most frequent and most serious adverse events by body system.

8.6 Type and Duration of Follow-up of Subjects after Adverse Events

Adverse events will be followed by the investigator or a clinician member of the study team in person if the subject is hospitalized for an AE or SAE. If the subject is not hospitalized, the investigator or a clinician may review the subject’s medical record, contact the subject by phone, or contact the subject’s primary care physician for follow-up.

Subjects withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator. Refer to Section 8.2.4 for follow-up of AEs/SAEs. The medical monitor or study principal investigator must be notified if the AE may relate to overdose of study treatment.

8.7 Halting Rules

Subject safety data will be reviewed on an ongoing basis to monitor for halting criteria.

The study enrollment and dosing will be halted for a safety review by the BPCA DMC if serious adverse reactions occur in ≥ 2 subjects.

Furthermore, the NICHD, the IND sponsor, the DMC, and the investigators shall have the right to recommend termination of this study at their discretion. Possible reasons for termination of the study include, but are not limited to:

1. Adverse events
2. Unsatisfactory enrollment with respect to quantity or quality

The study may be placed on hold or terminated at a site(s) for the following reasons:

1. Inaccurate or incomplete data collection
2. Falsification of records
3. Failure to adhere to the protocol

8.8 Safety Oversight (Safety Monitor plus DMC)

This study will be overseen by the BPCA DMC, the NICHD, and the FDA. The DMC will review data from individual study subjects on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study subjects. This evaluation will also assess data quality and timeliness, subject recruitment, accrual, and retention. These reviews will allow the DMC to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DMC to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided.

Ad Hoc Meetings of the DMC: The DMC may convene an ad hoc meeting to discuss any issue of safety raised by an investigator, the IND sponsor, or a member of the DMC. At the discretion of the investigators, the sponsor, and DMC members, a non-serious AE that is 1) associated with the product and 2) does not meet the stopping rules criteria may be considered as a trigger for an ad hoc DMC meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCC or Duke Clinical Research Institute (DCRI) sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations, the DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan Site visits will be made at standard intervals as defined by the clinical monitoring plans and may be made more frequently as directed by the IND and funding sponsors. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Study Outcome Measures

10.1.1 Primary Outcome Measures

1) PK parameters after multiple IV doses of clindamycin:
    - Clearance (Cl)
    - Volume of distribution (Vd)
    - Area under the curve (AUCtau)

10.1.2 Secondary Outcome Measures

1) PK results of patients transitioned to oral clindamycin:
    - Oral apparent clearance (Cl/F)
    - Oral apparent volume of distribution (V/F)

2) Safety: Adverse events will be collected during and after study drug administration.

10.2 Sample Size Considerations

It is anticipated that 12 children will be enrolled and treated in each of the IV groups for each age strata, leading to a total sample size of 24 subjects. A sample size of 24 subjects will provide adequate precision in the CL/F PK parameter estimate. Assuming an inter-individual 40% coefficient of variation in the population CL parameter estimate after weight-based allometric scaling, a sample size of 24 subjects would provide a margin of error of ± 16% in the 95% confidence interval of the CL estimate.

10.3 Analysis Plan

Population for Analysis
All subjects that receive at least 1 dose of study drug will be included in the safety analysis. All subjects with at least 1 evaluable PK sample will be included in the PK analysis n. If subjects have < 3 timed PK samples, additional subjects may be enrolled to ensure appropriate analysis.

Statistical Methodology
Descriptive statistics, such as number of observations, mean, median, 95% confidence interval, standard deviation, standard error, minimum, and maximum, will be presented by cohort for continuous variables (such as age, weight, and BMI). Other descriptive statistics, such as counts, proportions, and/or percentages, will be presented by cohort group to summarize discrete variables (such as race and sex).**Demographics and Baseline Characteristics**
The number of subjects completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be

summarized. Variables include race, ethnicity, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized by age and BMI cohorts.

Laboratory data, such as hematology and serum chemistry data, will be tabulated by age and BMI cohorts. Continuous laboratory measurements will be described using univariate 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.

Interim PK Analyses

An interim PK analysis of each age cohort will be performed after approximately 4 subjects have been enrolled into that cohort. If an interim analysis suggests that PK data is required on more than 12 subjects in that age cohort to evaluate the PK of clindamycin in this population, approximately 4 additional subjects will be enrolled into that age group for a total of 16 subjects.

PK Analysis

Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance. The influence of covariates (i.e., TBW, BMI, lean body weight, adjusted body weight, IBW etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each subject. The plasma concentrations-time profiles of clindamycin will be presented in figure form by subject and cohort (age and weight/BMI). Descriptive statistics will be presented for continuous and categorical variables. A detailed description of PK/PD analyses can be found in the PK analysis plan. We will compare PK parameters in this study of obese children to non-obese children.

11 SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in clinical trials. “Authorization” is required from each research subject (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the subjects' families. Consent forms describing in detail the study procedures and risks are given to the subject's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the subject's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject's legal guardian and answer any questions that may arise. The subject's legal guardian will sign and date the informed consent document prior to the subject being enrolled in the study. The subjects' legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects' legal guardians for their records. The rights and welfare of the subjects will be protected by emphasizing to their legal guardians that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the subjects' risk to receive the investigational product. This new information will be communicated by the investigator to subjects' legal guardians who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and subjects' legal guardians will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the subject consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed.

By signing the informed consent form, the subject's legal guardian agrees that the subject will complete all evaluations required by the trial, unless the subject is withdrawn voluntarily or is terminated from the trial for any reason.

12.1 Assent Process (e.g., Minor)

When a study includes subjects who may be enrolled in the study only with the consent of the subject's legally acceptable representative (e.g., minors), the subject should be informed about the study to the extent compatible with the subject's understanding. If capable, the subject should assent and sign and personally date the IRB-approved written assent form (if applicable based on local IRB guidelines). The assent form describes (in simplified terms) the details of the study, study procedures, and risks. Assent forms do not substitute for the consent form signed by the subject's legally acceptable representative. Consult with the institution's policies regarding enrollment of subjects who are unable to provide informed consent for themselves.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record subject data. The CRF will be used for the recording of all historical subject information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator. Data collection forms will be derived from the CRFs and provided by the DCC.

According to ICH E6, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file (regulatory binder) at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- MOP (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives,

microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the Principal Investigator, Pediatric Trials Network, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 50, 45 CFR 46 and 21 CFR 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

15.2 Institutional Review Board

This protocol is to be reviewed in accordance with subpart D of 45 CFR 46. Prior to its implementation, this protocol, including any subsequent amendments, the informed consent form, assent form, and any materials or advertisements presented to subjects, must be approved by an IRB constituted according to FDA regulations 21 CFR 56.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's federal-wide assurance number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Informed Consent

The investigator will choose subjects in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, a subject's parent/legal guardian will sign one informed consent for study enrollment. All subjects' parents/legal guardians must sign an informed consent form that complies with the requirements of both 21 CFR 50 and HIPAA before the subject enters the trial. A consent form that complies with the requirements of 21 CFR 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the subject's protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see **Section 12**.

15.4 Subject Confidentiality

Subjects will be assigned unique code numbers and will not be identified by name. Subject confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. Clinical study sites will permit access to such records.

15.5 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments for 3 days following the last dose of study drug, unless there is an ongoing SAE for which the subject will be followed for up to 10 days after the last dose of study drug.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the CRFs and provided by the DCC to the sites to record and maintain data for each subject enrolled in the study that is not otherwise captured in the medical record. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the CRF should be consistent with the source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the source documents and CRFs.

16.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team in real time. The site data entry staff will ensure that they are accurate and complete, and will enter the data into AdvantageEDC^{SM} within 72 business hours of data acquisition. Serious adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee in real time, and entered into AdvantageEDC^{SM} within 24 hours of identification. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

16.2 Data Capture Methods

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

16.3 Types of Data

Data for this study will include demographic data, medical history, physical examination data including height/weight/BMI, safety, laboratory, and outcome measures including PK data.

16.4 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected quarterly.

16.5 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the Investigator for 10 years after the end of the study or per local/state regulations or until subjects reach 21 years of age, whichever is longer. Study information in a subject's medical records will be retained forever. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the PI when documents are no longer required to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the DCC's AdvantageEDC^{SM}.

A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB per their guidelines. The site principal investigator/study staff are responsible for knowing and adhering to their IRB requirements.

16.7 Subject Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in clinical trials. Authorization is required from each research subject (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 PUBLICATION POLICY

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

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

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research.

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APPENDIX I

CDC Male and Female Child BMI Percentile Charts

APPENDIX II

A. PROHIBITED DRUGS for ALL subjects:

1) CYP 3A4 potent inhibitors including:
   a. Cyclosporine
   b. Erythromycin, clarithromycin
   c. Itraconazole, ketoconazole
   d. Ritonavir, delavirdine, protease inhibitors
   e. Nefazodone, fluoxetine, gluvoxamine
   f. Verapamil and diltiazem
2) CYP 3A4 inducers
   a. Rifampin,
   b. Phenytoin
   c. Ritonavir
3) Other: St. John's Wart

B. PROHIBITED DRUGS (unless the subject was receiving these drugs prior to enrollment and was receiving clindamycin as part of routine care prior to enrollment):

1) Neuromuscular blocking agents: Clindamycin may enhance neuromuscular blocking effect.
   a. Atracurium
   b. Cisatracurium
   c. Pancuronium
   d. Rocuronium
   e. Succinylcholine
   f. Vecuronium

APPENDIX III

Capsule Dosing Tables

WT_Low	WT_High		mg/kg/day_low	mg/kg/day_high	Goal	Total Daily Dose
20	20	150/150/150/150	30.0	30.0	30 mg/kg/day	600
21	30	300/300/300	30.0	42.9	30 mg/kg/day	900
31	40	300/300/300/300	30.0	38.7	30 mg/kg/day	1200
41	45	450/450/450	30.0	32.9	30 mg/kg/day	1350
46	60	450/450/450/450	30.0	39.1	30 mg/kg/day	1800
61	72	750/750/750	31.3	36.9	30 mg/kg/day	2250
73	80	600/600/600/600	30.0	32.9	30 mg/kg/day	2400
	>81	900/900/900				2700
20	25	300/300/300	36.0	45.0	40 mg/kg/day	900
26	32	300/300/300/300	37.5	46.2	40 mg/kg/day	1200
33	38	450/450/450	35.5	40.9	40 mg/kg/day	1350
39	48	450/450/450/450	37.5	46.2	40 mg/kg/day	1800
49	56	750/750/750	40.2	45.9	40 mg/kg/day	2250
57	64	600/600/600/600	37.5	42.1	40 mg/kg/day	2400
	>64	900/900/900				2700

APPENDIX IV

Clindamycin in Non-Obese Children

Ref	*PO clindamycin:*			*Dose 1*		*Dose 13*	*Dose 17*		
	Dose Amount	Age range (years)	*No. Subjects*	C_{max} (1 hour) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{max} (1 hour) (mcg/mL)	Half-life (h)	AUC (mcg/mL * h)
14	2 mg/kg	7-12	11	1.24 (0.70)	0.19 (0.27)	0.72 (0.21)	2.46 (0.68)	1.51 (0.74)	4.64 (2.11)
14	3 mg/kg	6-12	11	2.25 (0.53)	0.44 (0.19)	1.23 (0.31)	2.98 (0.93)	1.98 (0.60)	9.28 (2.71)
14	4 mg/kg	8-14	10	2.44 (0.65)	0.51 (0.25)	1.45 (0.36)	3.79 (0.61)	2.22 (0.78)	9.35 (3.23)
14	2 mg/kg	3-7	13	1.22 (0.51)	0.18 (0.23)	0.55 (0.17)	2.21 (0.51)	-	-
14	2 mg/kg	0.5-2	8	1.22 (1.14)	0.30 (0.37)	0.60 (0.32)	2.53 (0.86)	-	-
	IV clindamycin:			*Dose 1*					
				C_{max}	Half-life (h)				
5	5-7mg/kg	"Pediatric Patients"		10	2.5				

* all values are means (standard deviation)
C_{max} – maximum concentration
C_{min} – minimum concentration
AUC – area under the concentration time curve

Pediatric Trials Network

Pharmacokinetics and Safety Profile of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLN01

Phase I Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding Mechanism: Task Order

Protocol Number:	NICHD-2012-CLN01
Protocol Date:	06-MAR-2013
Protocol Version:	4.0
IND Number:	115,396 (P. Brian Smith, IND holder)
Principal Investigator:	Michael J. Smith, M.D., M.S.C.E. Assistant Professor of Pediatrics University of Louisville Louisville, KY 40202 Telephone: Redacted Fax: Redacted E-mail: Redacted

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to, 45 CFR 46 (Human Subjects Protection, incorporating Subpart D: Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D: Additional Safeguards for Children in Clinical Investigations), and 21 CFR 56 (Institutional Review Board [IRB]).

All individuals responsible for the design and/or conduct of this study have completed human subjects protection training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

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

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

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

Redacted

Principal Investigator Name (Print)

Redacted

Principal Investigator Signature

7 OCTOBER 2013

Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

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

Principal Investigator
Pediatric Trials Network Study

Site Principal Investigator Signature | Date

TABLE OF CONTENTS

SUPPLEMENTS/APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BPCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cl	Clearance
Cl/F	Oral Apparent Clearance
CRF	Case Report Form
CYP	Cytochrome
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
ECLS	Extracorporeal Life Support
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mg	Milligram
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*
N	Number (typically refers to participants)
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NPO	Nothing by Mouth
PD	Pharmacodynamics
PG	Pharmacogenomic
PK	Pharmacokinetics
PO	Oral
PTN	Pediatric Trials Network
SAE	Serious Adverse Event
$T_{1/2}$	Half-life
TBW	Total Body Weight
Vd	Volume of Distribution
V/F	Oral Apparent Volume of Distribution

PROTOCOL SYNOPSIS

Protocol Title:	Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLN01
Phase:	I
Product:	Clindamycin phosphate (intravenous) Clindamycin hydrochloride (oral capsules) Clindamycin palmitate (oral solution)
Objectives:	Primary: Determine the pharmacokinetics (PK) of intravenous clindamycin in overweight and obese children and adolescents Secondary: 1) Determine the PK of oral clindamycin in overweight and obese children and adolescents 2) Characterize the safety profile of clindamycin in overweight and obese children and adolescents
Study Design:	Prospective, multi-center, open-label, multiple-dose PK study of intravenous and oral clindamycin
Study Population:	Children ages 2 – <18 years of age with body mass index (BMI) ≥85 percentile for age
Number of Participants:	24–32 evaluable participants
Number of Sites:	Up to 6 sites
Duration of Subject Participation:	Up to 18 days (1-day screening period, minimum of 2 doses prior to PK samples and maximum of 14-day treatment period, and 3-day observation period after study drug administration to monitor for serious adverse events)
Dose Schedule:	30–40 mg/kg/day dosed every 6 or every 8 hours with a maximum daily dose of 2.7 grams/day. Dosing greater than 2.7 g/day will be allowed for children receiving clindamycin as standard of care.
Estimated Start:	October 2012
Estimated Time to Complete Enrollment:	Approximately 24 months
Inclusion Criteria:	1) 2 years – <18 years of age at the time of first dose of study drug 2) Suspected or confirmed infection OR receiving intravenous clindamycin per routine care 3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug 4) BMI ≥85th percentile for age and sex, based on CDC recommendations 5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

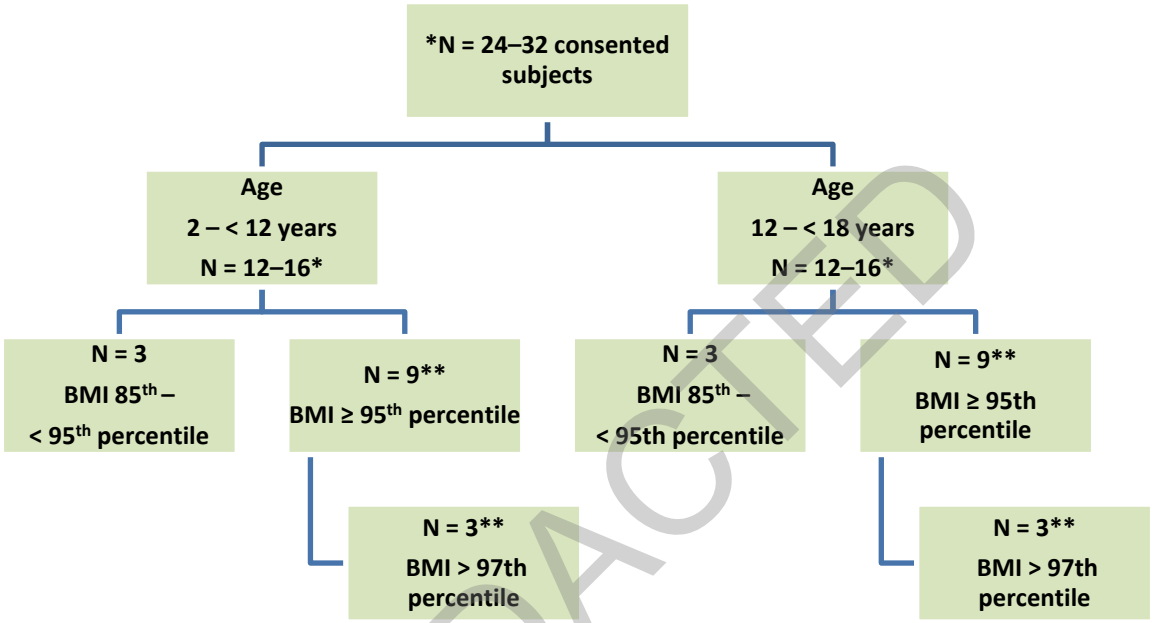
Exclusion Criteria:	1) The following apply only to those who are NOT already receiving clindamycin per routine care: a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin b. History of *C. difficile* colitis with previous administration of clindamycin c. AST >120 units/L d. ALT >210 units/L e. Total bilirubin >3 mg/dL f. Serum creatinine >2 mg/dL g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II.B**) 2) Previous participation in the study 3) Current exposure to medication listed in **Appendix II.A** 4) Participant is receiving extracorporeal life support (ECLS) 5) Participant is post-cardiac bypass (within 24 hours) 6) Participant on inotropes/pressors 7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

Table 1. Study Event Table

Study event/day	Screening/ study day 0	Study day 1 (any dose after the 1st dose of IV clindamycin; oral PK with 4th dose or later)	Study day 2–14	End of therapy (day 14) OR early withdrawal or discontinuation	3-Day post-treatment phone follow-up
Informed consent/ assent & HIPAA	X				
Medical history	X				
Demographics	X				
Concomitant medications of interest	X	X	X	X	X
Infection history	X	X			
Physical examination	X			X	
Weight	X				
Height	X				
BMI	X				
Waist:hip ratio	X				
Laboratory evaluation[a]	X			X	
α-1 glycoprotein (will be done by OpAns at their lab)[b]	X				
Laboratory evaluation (**6.6.1 Table 2**—if obtained as part of routine care)		X	X		X
Serum pregnancy test (female only)	X				
Feeding status (during PO PK portion only)		X			
Discarded scavenged samples[c]		X	X	X	
Clindamycin IV or PO[d]	X	X	X[f]		
PK samples[e]		X			
AE/SAE	X	X	X	X	X

[a]Hemoglobin, hematocrit, platelets, white blood cells, sodium, potassium, chloride, bicarbonate, total calcium, glucose, creatinine, blood urea nitrogen, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin.
[b]Central laboratory will measure this from plasma sample collected per PK schedule.
[c]Discarded blood cells may be collected at any time during the study.
[d]Group assignment (see **Figure 1**).
[e]PK sampling (**Table 3**, see **Section 6.6.2**).
[f]IV clindamycin will be continued per treating physician; when switched to PO, participant will participate in PO PK study.

Figure 1. Schematic/Description of Study Design



*IV participants who transition to oral clindamycin will participate in the oral PK study.
**Minimum of 3 participants with BMI > 97th percentile in each age group.

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Over the past decade, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a leading cause of hospitalization for children and adolescents in the United States (1). Consequently, the use of antimicrobial agents active against MRSA has become more prevalent (2). Specifically, the use of clindamycin among children hospitalized with *Staphylococcus aureus* infections increased from 21% in 1999 to 63% in 2008. At the same time, rates of childhood obesity have continued to remain high. Recent national data demonstrate that 17% of children aged 2–19 years in the United States are obese (body mass index [BMI] ≥ 95th percentile) and 12.3% are morbidly obese (BMI ≥ 97th percentile) (3). Obese patients have a greater likelihood of complications from infectious diseases and are at increased risk of developing *Staphylococcus aureus* infections. Therefore, an understanding of the PK of clindamycin in this population is critical to ensure appropriate interventional therapy.

Clindamycin, a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin (4), is approved by the U.S. Food and Drug Administration (FDA) for the treatment of pediatric and adult patients with respiratory tract, female pelvis and genital tract, and skin and soft tissue infections with susceptible bacteria including streptococci, pneumococci, and staphylococci. Clindamycin is also approved in adults for septicemia and intra-abdominal and serious infections with susceptible anaerobic bacteria (5).

Clindamycin is approximately 90% protein-bound. It is metabolized by the liver and excreted via the liver, bile, and kidneys. Impaired renal function modestly decreases the elimination of clindamycin; however, dosage adjustment is not required with renal dysfunction (4). Clindamycin phosphate (intravenous [IV] formulation) is rapidly converted to active clindamycin which has an elimination half-life of about 3 hours in adults and 2.5 hours in children (5). The drug penetrates well into all tissues, with the exception of the brain and cerebral spinal fluid. It is actively taken up and concentrated within the phagocytic cells. Clindamycin binds to the 50S subunit on the bacterial ribosome and inhibits protein synthesis by interfering with the formation of initiation complexes, thus inhibiting exotoxin production (4). Clindamycin exhibits time-dependent killing; and efficacy is correlated with the time clindamycin concentrations exceed the minimum inhibitory concentration of the pathogen of interest. A summary of clindamycin serum concentrations in non-obese children is found in **Appendix IV**.

Variability in serum and tissue concentrations has been reported in obese patients (4). The underlying premise is that this is due to physiologic changes that alter a drug's volume of distribution (Vd) and body clearance (Cl) (6,7). Thus, obese patients may be dosed inappropriately if fixed or "adult" doses are used (under-dosed) or if weight-based dosing is used (over-dosed) (6,7). Because critically ill obese patients with infections are reported to have a worse outcome than non-obese patients (8), it is imperative to determine if the disposition of and response to clindamycin may be altered compared to healthy children with an infection. In addition, sub-therapeutic drug concentrations may increase the development of resistant organisms. Thus, it is important to perform pharmacokinetic (PK) and pharmacodynamic (PD)

studies in the obese pediatric population to ensure that these patients are being optimally dosed with medications designed to treat infections. There are no currently available PK (or PD) data to guide clindamycin dosing in obese pediatric or adult patients. This proposal will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years.

2.2 Scientific Rationale

Selection of the correct drug dose and dose regimen is the most important decision in ensuring optimal pharmacotherapy. Defining an optimal regimen requires a clear understanding of the drug's PK, PD, and, for many compounds, pharmacogenomic (PG) profiles. Understanding these characteristics for drugs used in pediatrics is imperative to determine optimal dose regimens across the pediatric age continuum.

Clinically, drug dosing in pediatrics is individualized to age by basing the drug dose on a patient's body weight and the dose interval on the functional capacity of the drug's clearance pathways. This approach assumes, though inaccurately, that a drug's Vd and body Cl are directly proportional to a patient's body weight. Despite this lack of proportionality, the majority of pediatric patients favorably respond to weight-based drug dosing. However, as the potency of newer drugs increases and the need for more precise drug dose regimens expands, better-defined dose regimens based on careful assessment of the drugs' integrated PK-PD-PG profiles across the pediatric age continuum are needed (9). Complicating this paradigm are the substantially increasing numbers of children and adolescents who are obese, and even morbidly obese, and the lack of data on disposition in the obese population. Clinical trials of new drugs focused on FDA labeling exclude obese patients, leaving the determination of dosing regimens in the obese for post-marketing, often investigator-initiated studies.

Antibiotic Dosing Regimens Based on PK-PD Modeling
Prior to our understanding of the integrated PK-PD characteristics for antibiotic drugs, antibiotic dosing regimens were mostly based on perceived maximum tolerated doses often related in some manner to the target pathogen minimum inhibitory concentration (MIC). Integration of an antibiotic's PK with PD allows for the determination of the optimal dose regimen across the spectrum of antibiotic drugs (10,11). In addition, this more quantitative approach permits comparisons of different antibiotic drugs for a specific infection and far more accurate predictability of patient response. The specific antibiotic PK-PD characteristic used to predict outcome (i.e., bacteriologic eradication) appears to be mostly dependent on whether the drug's bacterial killing is concentration- or time-dependent. Clindamycin is most often described as a "time-dependent antibiotic with moderate persistent effects," and as such, the best predictor of bacterial killing appears to be the ratio of the area under the clindamycin (free, unbound) drug concentration time curve (AUC) divided by the targeted pathogen MIC (i.e., fAUC/MIC) (11). To accurately determine this pivotal PK-PD parameter, what is needed is a comprehensive understanding of the drug's PK profile across the age spectrum while incorporating the spectrum of pathophysiologic changes and differing body habitus. For clindamycin, these data are not available.

Clindamycin Pharmacokinetics
Limited published clindamycin PK data exist and encompass < 100 neonates, infants, and children. In neonates, clindamycin elimination is delayed compared with older infants and children—mean elimination half-life (t ½) values of 8.7 vs. 3.6 hours, respectively (12,13). Regardless of age group studied, variability was observed in clindamycin t ½, Vd, AND systemic

Cl. In addition, some studies report variable serum clindamycin concentrations (bioactivity) following parenteral dosing (12,14). Despite this variation in drug disposition, which is observed in both children and adults, bioactive serum clindamycin concentrations remain therapeutic following routine parenteral (intramuscular, IV) or oral dosing. Considering that clindamycin, an antibiotic, is used to treat infections caused by susceptible pathogens responsible for infectious diseases regardless of patient age, pediatric clindamycin development strategies need only focus on the drug's safety and PK profile to ensure similar systemic exposure. Available clindamycin PK data support close similarity for clindamycin systemic exposure (i.e., bioactive serum clindamycin concentrations and AUC) in older infants, children, and adults following comparable mg/kg doses (12, 14–19). As noted above, clindamycin PK in premature and full-term infants is, as expected, different than that observed in older patients (12,13). This foundation of data underscores the importance of studying clindamycin disposition in the obese pediatric patient.

Clindamycin is extensively bound to plasma protein, primarily to alpha 1 acid glycoprotein, and, with the exception of the brain or cerebrospinal fluid, effectively penetrates body tissues and fluids. The drug is metabolized primarily by the cytochrome (CYP) P450 isoenzyme CYP3A4 to two primary, antimicrobial active metabolites, a sulfoxide and to a lesser extent N-demethylclindamycin (20). Although only limited data are available for current clindamycin pediatric dosing regimens, the regimens employed clinically have been used for decades with apparent success. Nevertheless, clindamycin optimal dosing regimens in pediatrics remain unknown. Furthermore, the influence of obesity on clindamycin disposition is unknown and may have a far greater negative impact on patient outcome due to ill-defined, clinically extrapolated dosing.

Drug Dosing and Obesity

Data defining optimal drug dosing in the obese and morbidly obese adult patient are very limited and virtually non-existent in pediatrics. Drug dosing on total body weight (TBW) in the obese patient has the real risk of overdosing the patient, resulting in an increased incidence of adverse effects, while dosing on ideal body weight (IBW) can lead to serious under-dosing. In obese adults, IBW is increased by 20–40%, which is unaccounted for when using the many mathematical formulas available to calculate dosing based on a person's IBW. This deficiency may partially explain the inaccuracy of drug dose regimens for obese patients based on IBW formula estimations (21–26).

The influence varying degrees of obesity have on important physiologic functions across the age continuum in pediatrics is unknown. In adults, sparse data suggest that obese adults may have altered tissue blood flow rates due to inherent differences in blood flow to lean (greatest amount) and adipose tissue, impaired cardiac function, and alterations in phase I and II metabolism. Although intuitive, one might assume that a drug's Vd would be increased in obese patients for lipophilic compounds, though in fact, for the few drugs assessed, the Vd is highly variable. Similarly, Cl is also highly variable in the obese population, underscoring the need to determine drug disposition characteristics not only across the age continuum but also with increasing degrees of obesity (21–24). No such data are available for the pediatric patient, but these data combined underscore the need to critically assess a drug's disposition relative to age and body habitus. Furthermore, for antibiotics whose efficacy is dependent on achieving effective concentrations at the infectious site, interfaced with the organism, optimal dosing in the obese pediatric patient must be defined (6,7).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of Blood Draws
There are small risks to blood sampling, usually some pain/discomfort with the blood stick. Every effort will be made to avoid additional (to standard of care) sticks for this study by timing clinical blood draws to coincide with timed samples when possible and the use of existing IV lines when feasible for the blood draws.

Risks of Clindamycin
From the FDA label and review of the literature, the following are adverse reactions of clindamycin: antibiotic-associated colitis, pseudomembranous colitis, abdominal pain, nausea, and vomiting; hypersensitivity reactions (maculopapular rash and urticaria have been observed during drug therapy; generalized mild-to-moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions; rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin; a few cases of anaphylactoid reactions have been reported). Organ systems that are affected include skin and mucous membranes (pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported); liver (jaundice and abnormalities in liver function tests have been observed during clindamycin therapy); renal system (although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances); hematopoietic (transient neutropenia [leukopenia] and eosinophilia have been reported; reports of agranulocytosis and thrombocytopenia have been made; no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances); local reactions (pain, induration, and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion); musculoskeletal (rare instances of polyarthritis have been reported); cardiovascular (rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV administration). There is minimal additional risk to the participants who are receiving clindamycin as part of their routine medical care.

2.3.2 Known Potential Benefits

The participant may benefit from the use of the study drug; however, participation in this study has no other potential benefits to the participants. The results of this study may benefit overweight and obese participants in the future who require clindamycin therapy.

3 OBJECTIVES

Primary Aim
Characterize the PK of multiple-dose IV clindamycin in overweight and obese children and adolescents.

Secondary Aims
1. Characterize the PK of multiple-dose oral clindamycin in overweight and obese children and adolescents.
2. Characterize the safety profile of clindamycin in overweight and obese children and adolescents.

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1. PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUC_{tau})

3.1.2 Secondary Outcome Measures

1. PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2. Safety profile: Adverse events will be collected during and after study drug administration.

4 STUDY DESIGN

This will be a prospective, open-label PK and safety profile study of multiple doses of IV and oral clindamycin in overweight and obese children 2 – < 18 years of age. The total study duration is expected to be approximately 24 months; each participant will participate in the study for up to 18 days (screening day; treatment days 1–14 [may be as short as 2 days] followed by an observation period of 3 days post discontinuation of clindamycin therapy or after day 17 [on day 18] of therapy in those who are treated with more than 14 days of clindamycin).

5 Study Population

Selection of the Study Population

Eligible participants ages 2 – <18 years will be identified through the inpatient units at each participating site. There will be up to 32 evaluable participants (defined in **Section 10.3**) enrolled; however, target enrollment will be 24 participants. If dosing changes are suggested by the interim PK analysis (see **Section 10.3**), approximately 8 additional participants will be enrolled. Twelve to 16 participants will be enrolled in each of the following age groups: 2 – < 12 years and 12 – < 18 years of age. Participants will be further stratified into 1 of 2 groups based on their BMI (85th – <95th percentile, and ≥95th percentile). No more than 3 participants with BMI in the 85th – <95th percentile will be enrolled in each age group. Participating sites will prioritize enrollment of participants with BMI >97th percentile in each age group.

5.1 Inclusion/Exclusion Criteria

The investigator or other study site personnel will document in the source documents (e.g., the hospital chart) that informed consent and assent (if applicable) were obtained. Laboratory tests or non-pharmacologic treatment procedures that were performed and considered "routine care" within 72 hours of first dose of study drug may be used for screening procedures required by the protocol and recorded in the case report form (CRF).

Inclusion Criteria

1) 2 years – < 18 years of age at the time of first dose of study drug
2) Suspected or confirmed infection OR receiving IV clindamycin per routine care
3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug
4) BMI ≥ 85th percentile for age and sex, based on CDC recommendations
5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

Exclusion Criteria

1) The following apply only to those who are NOT already receiving clindamycin per routine care:
   a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin
   b. History of *C. difficile* colitis with previous administration of clindamycin
   c. AST > 120 units/L
   d. ALT > 210 units/L
   e. Total bilirubin > 3 mg/dL
   f. Serum creatinine > 2 mg/dL
   g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II.B**)
2) Previous participation in the study
3) Current exposure to medication listed in **Appendix II.A**
4) Participant is receiving extracorporeal life support (ECLS)
5) Participant is post-cardiac bypass (within 24 hours)

6) Participant on inotropes/pressors
7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

5.2 Treatment Assignment Procedures

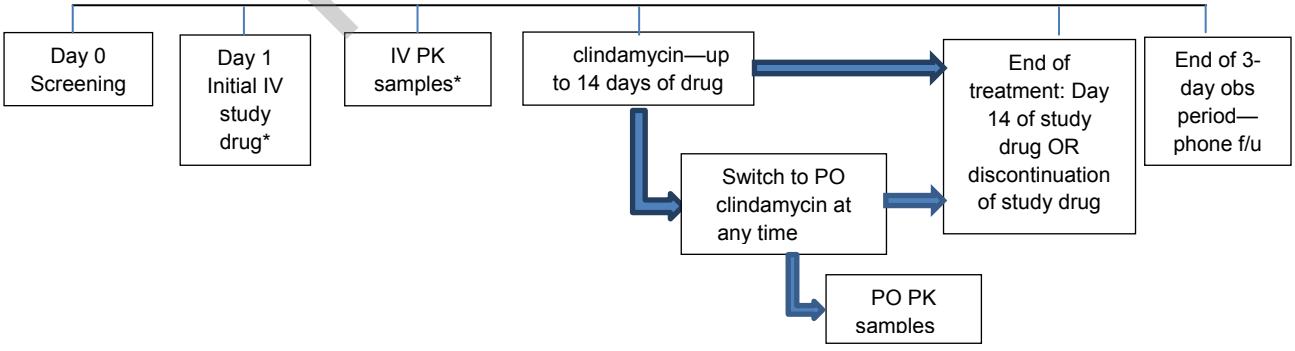
This will be an open-label PK study. Participants will be assigned to age groups based on age upon first dose of study drug and to a BMI group based on BMI at study entry.

5.2.1 Duration of Study Participation

Duration of therapy will be up to 14 days for children who receive the first dose of clindamycin as the study drug. All participants will begin on IV therapy and must receive at least 2 doses of IV clindamycin to participate in the study. The total duration of therapy with clindamycin will be determined by the treating physician for those children who are receiving clindamycin as part of routine care; however, only 14 days of therapy from the time of enrollment will be considered as study drug. If therapy extends beyond 14 days, the study follow-up visit/call will occur on approximately day 18 (+/– 1 day) (after completion of 3 safety observational days). Patients who are receiving antimicrobial agents other than clindamycin may enroll in this study and receive up to 3 doses of IV clindamycin and 4 doses of oral clindamycin in addition to their standard of care therapy. Participants who transition to oral clindamycin may return as outpatients to complete the PK portion of the study.

Total duration of study participation will be up to 18 days. This will comprise a 1-day screening period; a minimum 2 doses of IV and 4 doses of oral clindamycin before PK sampling begins for IV and oral routes, respectively; a maximum 14-day treatment period; and a 3-day post-study observation period to monitor for serious adverse events. The 3-day post-treatment visit may be a phone follow-up. Patients may continue clindamycin per their physician's recommendation after they have completed participation in this (maximum of) 18-day study.

Figure 2.Timeline



*Minimum of 2 doses of IV clindamycin before IV PK period.
**Minimum of 4 doses of PO clindamycin before PO PK period.

5.2.2 Replacement Participants

Participants in the IV portion of this study who are unable to provide at least 3 timed PK samples may be replaced.

5.2.3 Reasons for Participant Withdrawal

A participant or his/her parent/guardian may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the participant from participating in this study at any time. Participants may be prematurely discontinued from the study for any of the following reasons:

- Participant or investigator noncompliance with the study protocol
- At the request of the participant, investigator, treating physician, or sponsor
- Adverse reaction or suspected adverse reaction.

Participants are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. The participant who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations, and will be provided appropriate care under medical supervision until the symptoms of any adverse event (AE) resolve or the participant's condition becomes stable. Participants withdrawn from the study due to an AE must be followed per protocol (see **Section 8.2.4**).

5.2.4 Termination of Study

This study may be terminated at any time by NICHD, the Investigational New Drug Application (IND) sponsor, or the Data Monitoring Committee (DMC) if serious adverse reactions occur in 2 or more participants that are directly related to study drug, or if, in NICHD's judgment, there are no further benefits to be achieved from the study. A study site may be terminated if the investigator does not adhere to the study protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

See the schedule of study events and procedures (**Table 1**).

1. Medical history will be obtained by interview with the parent/legal guardian/participant and from the participant's medical records.

2. Concomitant medications of interest administered within 7 days prior to first study dose and during the period of administration of study drug, including herbal products of interest, will be recorded (see **Appendix II**).

3. Physical examination, including abnormal physical findings, height (measured standing if possible), weight and waist:hip ratio will be obtained. NOTE: The initial physical examination information (except the height, weight, and waist/hip measurements) may be obtained from the medical record but must have been performed within 24 hours prior to enrollment. BMI will be calculated from height and weight using the following formula: BMI = [weight (kg) / (stature (cm))^2] x 10,000. Refer to the Centers for Disease Control (CDC) pediatric BMI calculator (http://apps.nccd.cdc.gov/dnpabmi/) to determine the BMI. The BMI percentile will be obtained using the BMI calculator and verified using the age- and sex-specific CDC BMI charts (**Appendix I**).

4. The safety laboratory testing will be performed at each site's local laboratory. Baseline laboratory values may be used if obtained as part of routine care within 72 hours prior to study enrollment. The serum pregnancy test will also be performed at the local laboratory (within 24 hours prior to study enrollment). Alpha-1-glycoprotein will be measured by OpAns at their laboratory using plasma already collected as part of the PK sample collection.

5. PK samples will be obtained after at least 2 IV doses of clindamycin are completed and after 4 doses of oral clindamycin (see **Section 6.6.2**).

6.2 Screening

Research staff at sites will screen potential participants for eligibility requirements per local institutional policies.

6.3 Enrollment/Baseline

Baseline/Pre-Dose Assessment (Day 0)
After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA documents, the participant has signed assent (if applicable), and after it has been determined

that the participant satisfies all inclusion and no exclusion criteria, the following evaluations will be performed and recorded in the CRF:

1. Participant demographics
2. Physical examination, including weight, height, waist:hip ratio, and BMI
3. Pertinent medical history
4. Concomitant medications of interest (7 days prior to first dose of study drug) (see **Appendix II**)
5. Laboratory determinations (see **Table 2**, **Section 6.6.1**)
6. Culture results of blood, urine, sputum, or wound (if obtained as part of routine care) within 72 hours prior to the first dose of study drug
7. For participants receiving clindamycin per routine care, the date and time for the doses administered prior to first dose of study drug will be recorded (up to a maximum of 6 prior doses)
8. Serum pregnancy test (females only who have reached menarche) within 24 hours of study enrollment

Assessments/Procedures (Days 1–14)
The participant will start study drug upon completion of the pre-assessment, or, if s/he was already receiving clindamycin (at the study-recommended dose), s/he will continue receiving that dose of clindamycin. If s/he was receiving clindamycin at a dose lower than the study-recommended dose, the dose will be changed to be in compliance with the protocol. Total body weight will be used to calculate the absolute dose administered. Refer to **Section 7.1.2** for dosing. Participants who transition to oral therapy will also participate in the oral-dose PK portion.

The following assessments will be conducted after the participant receives the first dose of clindamycin after study enrollment and throughout therapy up to day 14:

1. Concomitant medications of interest (see **Appendix II**)
2. Start date/time and stop date/time of clindamycin administration and flush date/stop time after IV administration
3. Feeding status (during PO PK portion only): nothing by mouth (NPO), clear liquids, full feeds, etc.
4. Collection of PK samples (including date/time) (see **Section 6.6.2**)
5. Results for laboratory tests of interest (see **Section 6.6.1**)
6. Collection of culture results (if available)
7. Adverse events (see **Section 8.2.1**)

6.4 End of Therapy OR Early Withdrawal/Discontinuation

The following assessments will be conducted at early withdrawal or end of therapy:

1. Concomitant medications of interest (see **Appendix II**)
2. Physical examination
3. Laboratory evaluations (see **Section 6.6.1**)
4. Adverse events (see **Section 8.2.1**)

6.5 Follow-up Safety Phone Call

Assessments/Procedures (Day 3 Post Treatment): This visit will be a phone follow-up unless the participant is still hospitalized. This assessment must occur at least 72 hours but no more than 96 hours after the last dose of study drug. The following information will be obtained:

1. Adverse events (see **Section 8.2.1**)
2. Concomitant medications of interest (**Appendix II**)
3. Any labs collected

6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

Laboratory testing (**Table 2**) will be collected on all participants and be performed in the local laboratory at each site. Laboratory values will be collected within 72 hours prior to enrollment. Laboratory values performed as part of routine care within 72 hours prior to enrollment may be used for baseline laboratory tests. Laboratory values will also be obtained at the end of therapy. Laboratory values obtained within ± 24 hours of discontinuation of study drug or within ± 24 hours of completion of 14 days of study drug (if they are continuing clindamycin beyond 14 days) may be used as end-of-treatment laboratory values. If these laboratory tests have not been performed as part of routine care, they will be performed for the study per the protocol schedule. The serum pregnancy test will also be performed at the local laboratory. Alpha (α)-1-glycoprotein will be measured from one of the PK samples by the central laboratory once during the study using an ELISA kit (central laboratory). Sites do not need to collect an extra sample to measure α-1-glycoprotein.

Table 2. Laboratory Evaluations

Hematology	Serum Biochemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Platelets	Chloride
White blood cells	Bicarbonate
	Total calcium
	Glucose
	Creatinine
	Blood urea nitrogen
	Total protein
	Albumin
	Aspartate aminotransferase
	Alanine aminotransferase
	Bilirubin

6.6.2 Special Assays or Procedures

PK Samples
Blood (0.5 mL) will be collected with scheduled IV and oral doses of clindamycin for clindamycin plasma concentration determinations (see **Table 3** below for schedule). In participants receiving IV clindamycin, PK samples should be collected from a site separate from the site of administration. PK samples in participants on IV clindamycin will be collected with any dose after the first dose of study drug (excluding the first dose), and, for PO clindamycin, PK samples will be collected after the fourth dose or any dose after the fourth dose. The PK sampling will be drawn according to the following schedule relative to the end of infusion (IV PK) or actual time of oral administration (PO PK).

Table 3. PK Schedule

Scheduled PK Sampling Times				
Time (hours)*	**IV dose***		**PO dose**	
	Q6h	**Q8h**	**Q6h**	**Q8h**
Pre-dose 0 (within 15 minutes prior to the dose)	**X****	**X****	**X****	**X****
0.5 (± 5 minutes)	**X****	**X****	N/A	N/A
1–1.5	X	X	**X****	X**
3–4	**X****	**X****	**X****	--
5–6	--	X	--	**X****
Pre-dose (will depend if on q6h or q8h dose schedule)	**X****	**X****	**X****	**X****
Total number of samples	5	6	4	4

* Time starts at end of flush after the 30-minute infusion.
** Priority samples (see paragraph below).

Every effort should be made to collect all PK samples for each participant. Collection of PK samples should be timed with collection of laboratory tests per standard of care to minimize blood draws specifically for the study. If it is impractical to collect all PK samples during the same dosing interval, samples can be obtained at different dosing intervals. If it is impossible to obtain all PK samples for each participant, **PK samples can be prioritized to include:**

a) **For IV administration: pre-dose, 0.5 hours, 3–4 hours, and pre-next dose**
b) **For oral administration: pre-dose, 1–1.5 hours, 3–4 hours (q6h dosing), 5–6 hours (q8h dosing), and pre-next dose**

Clindamycin concentrations in plasma will be measured at a central laboratory using a validated bioanalytical assay. In addition, scavenged samples will be obtained.

Scavenged Plasma Sampling
Plasma samples collected in EDTA tubes during the course of therapy (~100 µL plasma or ~200 µL whole blood) will be procured, after consent. A maximum of 10 scavenged plasma samples will be collected per participant. Collection may begin with any specimen collected after the first dose of study drug through 24 hours after the last dose of study drug. The date and time of

sample collection, as well as the date and time the sample is frozen, will be collected for all scavenged samples.

Minimizing Blood Loss
To minimize the amount of blood sampling, laboratory values will be obtained only at baseline and end of study. If they have been obtained as part of routine care within 72 hours prior to enrollment into the study, the baseline laboratory values do not need to be repeated. The PK sampling scheme will be employed such that no more than a total of 8 mL (< 3 mL/kg) of blood is obtained from each participant for PK analysis. Plasma samples will be collected in 0.5 mL blood aliquots.

6.6.3 Specimen Preparation, Handling, Storage, and Shipping

Detailed information for collection, labeling, preparation, handling, storage, and shipping of specimens is detailed in the manual of procedures (MOP).

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

A dose of 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 g/day is selected based on current labeling. Patients who are receiving clindamycin as part of their routine care are also eligible to participate if their dose can be adjusted to be at least 30 mg/kg/day upon enrollment. The dose administered will be based on TBW. Because bioavailability is estimated at 85%, the same dose will be used for oral administration as is used for IV dosing. Both solution and capsule preparations will be included in this study because both oral formulations are used in clinical practice, and it will allow the inclusion of those patients who cannot swallow pills. In the absence of PK data, we assume that drug clearance will be comparable in obese pediatric patients compared to non-obese pediatric patients. Therefore, a dosing regimen 30–40 mg/kg per day and a maximum dose of 2.7 g/day should provide exposures similar to those used in children and adolescents with a normal BMI. It is predicted to be safe in the obese population because similar doses are currently used per routine care.

7.1.2 Dose and Timing

Both q6h and q8h dosing will be allowed for both oral and IV dosing of clindamycin. For children receiving clindamycin as part of clinical care, this protocol will not prescribe a route of administration or dosing interval; the dose, route of administration, and dosing interval prescribed by the treating physician will be recorded on the CRF. Dosing greater than 2.7 g/day will be allowed for children receiving clindamycin as part of clinical care. However, if the prescribed dose is less than the lowest dose for this study, the dose of clindamycin will be changed to comply with the study-recommended dose. See **Section 5.2.1** for duration of therapy.

IV dosing: A minimum of 2 doses of IV clindamycin will be administered. The dose administered will be based on TBW at 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 grams/day. The drug will be administered over 30 (+/– 5) minutes. The venous access line will be flushed per local practice after completion of IV administration, and the time of the end of flush will be documented. It is preferred that the flush be ≤1 minute after the end of infusion.

Oral dosing: For those participants who are receiving clindamycin as a solution, they will receive 30–40 mg/kg/day divided q6h or q8h. For those participants receiving the capsule formulation, they will receive the dose of clindamycin defined in **Appendix III**. Only whole capsules will be used. The oral solution will be used for those participants who cannot swallow capsules. During the PO phase of the study, PK samples should be obtained after the fourth dose of PO clindamycin (but may be collected with a later dose if unable to do the fourth dose). No more than 12 PO study drug doses will be administered as part of this study.

7.1.3 Formulation, Packaging, and Labeling

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules.

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles for reconstitution.

Each formulation is approved for use in the United States.

7.1.4 Product Storage and Stability

Clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules), and clindamycin palmitate (PO oral solution) will all be stored at room temperature (20–25^0 C). Diluted clindamycin phosphate (IV) is stable at room temperature for at least 16 days and refrigerated for at least 32 days. Reconstituted clindamycin palmitate hydrochloride, USP for oral solution is stable for 2 weeks at room temperature and should not be refrigerated. See the MOP for detailed information.

7.2 Preparation and Administration of Study Intervention/Study Drug

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL. The drug will be infused over 30 (+/– 5) minutes. Infusion rates should not exceed 30 mg/minute. The pharmacy will prepare the IV formulation, and the dose administered will be based on TBW.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules, and the dose will be dispensed based on TBW (see **Appendix III** for dosing).

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles and will be prepared in the pharmacy at each site based on the reconstitution recommendation in the label. The dose administered will be based on TBW.

Refer to the MOP for additional details regarding drug procurement, drug preparation, and administration.

7.3 Modification of Study Intervention/Investigational Product for a Participant

No dosing adjustments are required for hepatic or renal impairment.

7.4 Accountability Procedures for the Study Intervention/Study Drugs

Each site will provide drug for their study participants. The study product accountability records will be maintained in the pharmacy study binder for clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules) and clindamycin palmitate (PO oral solution). See MOP for specific details related to investigational product accountability.

7.5 Assessment of Participant Compliance w/ Study Intervention

Compliance with dosing will be determined using the pharmacy accountability logs and the participant's medication administration record. For those participants who are discharged on oral clindamycin and have not completed the PO PK visit, the participant or parent/guardian will keep a drug administration diary and all drugs will be accounted for at the outpatient PK study visit.

7.6 Concomitant Medications of Interest/Treatments

Concomitant medications of interest are listed in **Appendix II**. Children who are prescribed one of these medications after enrollment may continue in the study.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

AEs will be collected during and after study drug administration and for 3 days following end of therapy with clindamycin. Results will be tabulated by MedDRA System Organ Class and Preferred Term.

8.2 Methods & Timing for Assessing, Recording, & Analyzing Safety Parameters

AEs will be collected from the time of consent, throughout the period of study drug administration, and for 3 days following end of therapy with clindamycin. See **Section 8.6** for clarification for AEs identified at the 3-day follow-up visit and for serious AEs (SAEs). Safety will be assessed by frequency and incidence of AEs and SAEs. The Best Pharmaceuticals for Children Act (BPCA) safety monitoring committee (DMC) convened by NICHD will review data and safety information from study participants.

8.2.1 Adverse Event

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

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

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

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

1. Death
2. Life-threatening AE (“life-threatening” means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.2.2 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, investigational plan, or informed consent.

8.2.3 Identification of Events and Timeframe for Reporting

As all participants in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after consent has been obtained. The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome. Any event beginning more than 3 days after the last dose of study drug will not be captured.

8.2.4 Follow-up of Adverse Events

AEs ongoing at the time of the last dose of study drug will be followed up to 3 days after the last dose of study drug. AEs that resolve during the study or follow-up period will have the resolution date documented in the CRF. Adverse events that are identified at the last assessment visit/phone contact (or at the early termination visit) must be recorded on the AE CRF, with the status of the AE noted. Any events that are identified at the last assessment visit/phone contact will be followed for an additional 3 days for AEs and 10 days for SAEs and if still ongoing can be “resolved by convention”. All serious suspected adverse reactions will be followed until resolution. All enrolled participants in both cohorts who receive at least 1 dose of clindamycin will be followed for safety.

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. **MODERATE**: Participant experiences enough symptoms or findings to require intervention
3. **SEVERE**: Participant experiences symptoms or findings that require significant intervention

8.4 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction. ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.5 Reporting Procedures and Timeframe for Reporting

All AEs will be entered into the data system within 72 business hours of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties encountered when entering the event into the electronic data capture (EDC) system, the SAE will be reported to the data coordinating center (DCC) by telephone or FAX communication. Investigators must submit safety reports as required by their local IRB, independent of the reporting requirements specified in the protocol.

8.5.1 Serious Adverse Events

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC, IND sponsor, protocol chair, and funding sponsor (NICHD). The BPCA DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.5.2 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The sponsor or his representative will submit expedited safety reports (IND safety reports) to the FDA and other regulatory agencies as necessary, and will inform the DMC and investigators of such regulatory reports. Site investigators must submit IND safety reports as required by their IRB. Documentation of the submission to and receipt by the IRB should be retained for each IND safety report. The sponsor will submit a progress report of the investigation annually, which will include a summary showing the most frequent and most serious adverse events by body system.

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

Adverse events will be followed by the investigator or a clinician member of the study team in person if the participant is hospitalized for an AE or SAE. If the participant is not hospitalized, the investigator or a clinician may review the participant’s medical record, contact the participant by phone, or contact the participant’s primary care physician for follow-up.
Participants withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator. Refer to **Section 8.2.4** for follow-up of AEs/SAEs. The medical monitor or study principal investigator must be notified if the AE may relate to overdose of study treatment.

8.7 Halting Rules

Participant safety data will be reviewed on an ongoing basis to monitor for halting criteria.

The study enrollment and dosing will be halted for a safety review by the BPCA DMC if serious adverse reactions occur in ≥ 2 participants.

Furthermore, the NICHD, the IND sponsor, protocol chair, the DMC, and the investigators shall have the right to recommend termination of this study at their discretion. Possible reasons for termination of the study include, but are not limited to:

1. Adverse events
2. Unsatisfactory enrollment with respect to quantity or quality

The study may be placed on hold or terminated at a site(s) for the following reasons:

1. Inaccurate or incomplete data collection
2. Falsification of records
3. Failure to adhere to the protocol

8.8 Safety Oversight

This study will be overseen by the BPCA DMC, the NICHD, and the FDA. The DMC will review data from individual study participants on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study participants. This evaluation will also assess data quality and timeliness, participant recruitment, accrual, and retention. These reviews will allow the DMC to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DMC to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided.

Ad Hoc Meetings of the DMC: The DMC may convene an ad hoc meeting to discuss any issue of safety raised by an investigator, the IND sponsor, or a member of the DMC. At the discretion of the investigators, the sponsor, and DMC members, a non-serious AE that is 1) associated with the product and 2) does not meet the stopping rules criteria may be considered as a trigger for an ad hoc DMC meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCC or Duke Clinical Research Institute (DCRI) sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations, the DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan. Site visits will be made at standard intervals as defined by the clinical monitoring plans and may be made more frequently as directed by the IND and funding sponsors. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Study Outcome Measures

10.1.1 Primary Outcome Measures

1) PK parameters after multiple IV doses of clindamycin:
    - Clearance (Cl)
    - Volume of distribution (Vd)
    - Area under the curve (AUC_{tau})

10.1.2 Secondary Outcome Measures

1) PK results of patients transitioned to oral clindamycin:
    - Oral apparent clearance (Cl/F)
    - Oral apparent volume of distribution (V/F)

2) Safety: Adverse events will be collected during and after study drug administration.

10.2 Sample Size Considerations

It is anticipated that 12 children will be enrolled and treated in each of the IV groups for each age strata, leading to a total sample size of 24 participants. A sample size of 24 participants will provide adequate precision in the Cl/F PK parameter estimate. Assuming an inter-individual 40% coefficient of variation in the population Cl parameter estimate after weight-based allometric scaling, a sample size of 24 participants would provide a margin of error of ± 16% in the 95% confidence interval of the Cl estimate.

10.3 Analysis Plan

Population for Analysis
All participants that receive at least 1 dose of study drug will be included in the safety analysis. All participants with at least 1 evaluable PK sample will be included in the PK analysis plan. If participants have < 3 timed PK samples, additional participants may be enrolled to ensure appropriate analysis.

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

Demographics and Baseline Characteristics
The number of participants completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be summarized. Variables include race, ethnicity, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized by age and BMI cohorts.

Laboratory data, such as hematology and serum chemistry data, will be tabulated by age and BMI cohorts. Continuous laboratory measurements will be described using univariate 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.

Interim PK Analyses
An interim PK analysis of each age cohort will be performed after approximately 4 participants have been enrolled into that cohort. If an interim analysis suggests that PK data is required on more than 12 participants in that age cohort to evaluate the PK of clindamycin in this population, approximately 4 additional participants will be enrolled into that age group for a total of 16 participants.

PK Analysis
Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance. The influence of covariates (i.e., TBW, BMI, lean body weight, adjusted body weight, IBW, etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each participant. The plasma concentrations-time profiles of clindamycin will be presented in figure form by participant and cohort (age and weight/BMI). Descriptive statistics will be presented for continuous and categorical variables. A detailed description of PK/PD analyses can be found in the PK analysis plan. We will compare PK parameters in this study of obese children to non-obese children.

11 PARTICIPANT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. “Authorization” is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the participants' families. Consent forms describing in detail the study procedures and risks are given to the participant's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the participant's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant's legal guardian and answer any questions that may arise. The participant's legal guardian will sign and date the informed consent document prior to the participant being enrolled in the study. The participant's legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participant's legal guardian for their records. The rights and welfare of the participant will be protected by emphasizing to their legal guardian that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the participant's risk to receive the investigational product. This new information will be communicated by the investigator to participant's legal guardian who consented to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participant's legal guardian will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed.

By signing the informed consent form, the participant's legal guardian agrees that the participant will complete all evaluations required by the trial, unless the participant is withdrawn voluntarily or is terminated from the trial for any reason.

12.1 Assent Process (e.g., Minor)

When a study includes participants who may be enrolled in the study only with the consent of the participant's legally acceptable representative (e.g., minors), the participant should be informed about the study to the extent compatible with the participant's understanding. If capable, the participant should assent and sign and personally date the IRB-approved written assent form (if applicable based on local IRB guidelines). The assent form describes (in simplified terms) the details of the study, study procedures, and risks. Assent forms do not substitute for the consent form signed by the participant's legal guardian. Consult with the institution's policies regarding enrollment of participants who are unable to provide informed consent for themselves.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record participant data. The CRF will be used for the recording of all historical participant information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator. Data collection forms will be derived from the CRFs and provided by the DCC.

According to ICH E6, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file (regulatory binder) at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- MOP (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records

kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the principal investigator, Pediatric Trials Network, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 50, 45 CFR 46 and 21 CFR 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

15.2 Institutional Review Board

This protocol is to be reviewed in accordance with subpart D of 45 CFR 46. Prior to its implementation, this protocol, including any subsequent amendments, the informed consent form, assent form, and any materials or advertisements presented to participants, must be approved by an IRB constituted according to FDA regulations 21 CFR 56.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's federal-wide assurance number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Informed Consent

The investigator will choose participants in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, a participant's parent/legal guardian will sign one informed consent for study enrollment. All participants' parents/legal guardians must sign an informed consent form that complies with the requirements of both 21 CFR 50 and HIPAA before the participant enters the trial. A consent form that complies with the requirements of 21 CFR 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the participant's protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see **Section 12**.

15.4 Participant Confidentiality

Participants will be assigned unique code numbers and will not be identified by name. Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Clinical study sites will permit access to such records.

15.5 Study Discontinuation

If the study is discontinued, enrolled participants will continue to be followed for safety assessments for 3 days following the last dose of study drug, unless there is an ongoing SAE for which the participant will be followed for up to 10 days after the last dose of study drug.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the CRFs and provided by the DCC to the sites to record and maintain data for each participant enrolled in the study that is not otherwise captured in the medical record. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the CRF should be consistent with the source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the source documents and CRFs.

16.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team in real time. The site data entry staff will ensure that they are accurate and complete, and should enter the data into AdvantageEDC^{SM} within 72 business hours of data acquisition. Serious adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee in real time, and entered into AdvantageEDC^{SM} within 24 hours of identification. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

16.2 Data Capture Methods

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

16.3 Types of Data

Data for this study will include demographic data, medical history, physical examination data including height/weight/BMI, safety, laboratory, and outcome measures including PK data.

16.4 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected quarterly.

16.5 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the Investigator for 10 years after the end of the study or per local/state regulations or until participants reach 21 years of age, whichever is longer. Study information in a participant's medical records will be retained forever. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the PI when documents are no longer required to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the DCC's AdvantageEDC^{SM}.

A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB per their guidelines. The site principal investigator/study staff are responsible for knowing and adhering to their IRB requirements.

16.7 Participant Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 PUBLICATION POLICY

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

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

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research.

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APPENDIX I

CDC Male and Female Child BMI Percentile Charts

APPENDIX II – Medications of Interest

A. Exclusion for ALL participants at the time of enrollment:

1) CYP 3A4 potent inhibitors including:
   a. Cyclosporine
   b. Erythromycin, clarithromycin
   c. Itraconazole, ketoconazole
   d. Ritonavir, delavirdine, protease inhibitors
   e. Nefazodone, fluoxetine, fluvoxamine
   f. Verapamil and diltiazem
2) CYP 3A4 inducers
   a. Rifampin,
   b. Phenytoin
   c. Ritonavir
3) Other: St. John's Wart

B. Exclusion at the time of enrollment (unless the participant was receiving these drugs prior to enrollment AND was receiving clindamycin as part of routine care prior to enrollment):

1) Neuromuscular blocking agents: Clindamycin may enhance neuromuscular blocking effect.
   a. Atracurium
   b. Cisatracurium
   c. Pancuronium
   d. Rocuronium
   e. Succinylcholine
   f. Vecuronium

The above drugs are only excluded at the time of enrollment; if a participant begins taking any of the drugs while on-study, he/she will not be discontinued.

APPENDIX III

Capsule Dosing Tables

WT_Low	WT_High		mg/kg/day_low	mg/kg/day_high	Goal	Total Daily Dose
20	20	150/150/150/150	30.0	30.0	30 mg/kg/day	600
21	30	300/300/300	30.0	42.9	30 mg/kg/day	900
31	40	300/300/300/300	30.0	38.7	30 mg/kg/day	1200
41	45	450/450/450	30.0	32.9	30 mg/kg/day	1350
46	60	450/450/450/450	30.0	39.1	30 mg/kg/day	1800
61	72	750/750/750	31.3	36.9	30 mg/kg/day	2250
73	80 >81	600/600/600/600 900/900/900	30.0	32.9	30 mg/kg/day	2400 2700
20	25	300/300/300	36.0	45.0	40 mg/kg/day	900
26	32	300/300/300/300	37.5	46.2	40 mg/kg/day	1200
33	38	450/450/450	35.5	40.9	40 mg/kg/day	1350
39	48	450/450/450/450	37.5	46.2	40 mg/kg/day	1800
49	56	750/750/750	40.2	45.9	40 mg/kg/day	2250
57	64 >64	600/600/600/600 900/900/900	37.5	42.1	40 mg/kg/day	2400 2700

APPENDIX IV

Clindamycin in Non-Obese Children

Ref	*PO clindamycin:*			*Dose 1*		*Dose 13*	*Dose 17*		
	Dose Amount	Age range (years)	*No. Subjects*	C_{max} (1 hour) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{max} (1 hour) (mcg/mL)	Half-life (h)	AUC (mcg/mL * h)
14	2 mg/kg	7-12	11	1.24 (0.70)	0.19 (0.27)	0.72 (0.21)	2.46 (0.68)	1.51 (0.74)	4.64 (2.11)
14	3 mg/kg	6-12	11	2.25 (0.53)	0.44 (0.19)	1.23 (0.31)	2.98 (0.93)	1.98 (0.60)	9.28 (2.71)
14	4 mg/kg	8-14	10	2.44 (0.65)	0.51 (0.25)	1.45 (0.36)	3.79 (0.61)	2.22 (0.78)	9.35 (3.23)
14	2 mg/kg	3-7	13	1.22 (0.51)	0.18 (0.23)	0.55 (0.17)	2.21 (0.51)	-	-
14	2 mg/kg	0.5-2	8	1.22 (1.14)	0.30 (0.37)	0.60 (0.32)	2.53 (0.86)	-	-
	IV clindamycin:			*Dose 1*					
				C_{max}	Half-life (h)				
5	5-7mg/kg	Pediatric patients”		10	2.5				

*All values are means (standard deviation).
C_{max} – maximum concentration; C_{min} – minimum concentration; AUC – area under the concentration time curve.

Pediatric Trials Network

Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLN01

Phase I Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding Mechanism: Task Order

Protocol Number:	NICHD—2012-CLN01
Protocol Date:	22-MAR-2013
Protocol Version:	5.0
IND Number:	115396 (P. Brian Smith, IND holder)
Principal Investigator:	Michael J. Smith, M.D., M.S.C.E. Assistant Professor of Pediatrics University of Louisville Louisville, KY 40202 Telephone: Redacted Fax: Redacted E-mail: Redacted

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to, 45 CFR 46 (Human Subjects Protection, incorporating Subpart D: Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D: Additional Safeguards for Children in Clinical Investigations), and 21 CFR 56 (Institutional Review Board [IRB]).

All individuals responsible for the design and/or conduct of this study have completed human subjects protection training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

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

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

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

_____
Principal Investigator Name (Print)

_____ _____
Principal Investigator Signature Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

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

Principal Investigator
Pediatric Trials Network Study

Site Principal Investigator Signature Date

TABLE OF CONTENTS

SUPPLEMENTS/APPENDICES

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BPCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cl	Clearance
Cl/F	Oral Apparent Clearance
CRF	Case Report Form
CYP	Cytochrome
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
ECLS	Extracorporeal Life Support
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mg	Milligram
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*
N	Number (typically refers to participants)
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NPO	Nothing by Mouth
PD	Pharmacodynamics
PG	Pharmacogenomic
PK	Pharmacokinetics
PO	Oral
PTN	Pediatric Trials Network
SAE	Serious Adverse Event
$T_{1/2}$	Half-life
TBW	Total Body Weight
Vd	Volume of Distribution
V/F	Oral Apparent Volume of Distribution

PROTOCOL SYNOPSIS

Protocol Title:	Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLN01
Phase:	I
Product:	Clindamycin phosphate (intravenous) Clindamycin hydrochloride (oral capsules) Clindamycin palmitate (oral solution)
Objectives:	Primary: Determine the pharmacokinetics (PK) of intravenous clindamycin in overweight and obese children and adolescents Secondary: 1) Determine the PK of oral clindamycin in overweight and obese children and adolescents 2) Characterize the safety profile of clindamycin in overweight and obese children and adolescents
Study Design:	Prospective, multi-center, open-label, multiple-dose PK study of intravenous and oral clindamycin
Study Population:	Children ages 2 – <18 years of age with body mass index (BMI) ≥85 percentile for age
Number of Participants:	24–32 evaluable participants
Number of Sites:	Up to 6 sites
Duration of Subject Participation:	Up to 18 days (1-day screening period, minimum of 2 doses prior to PK samples and maximum of 14-day treatment period, and 3-day observation period after study drug administration to monitor for serious adverse events)
Dose Schedule:	30–40 mg/kg/day dosed every 6 or every 8 hours with a maximum daily dose of 2.7 grams/day. Dosing greater than 2.7 g/day will be allowed for children receiving clindamycin as standard of care.
Estimated Start:	October 2012
Estimated Time to Complete Enrollment:	Approximately 24 months
Inclusion Criteria:	1) 2 years – <18 years of age at the time of first dose of study drug 2) Suspected or confirmed infection OR receiving intravenous clindamycin per routine care 3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug 4) BMI ≥85th percentile for age and sex, based on CDC recommendations 5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

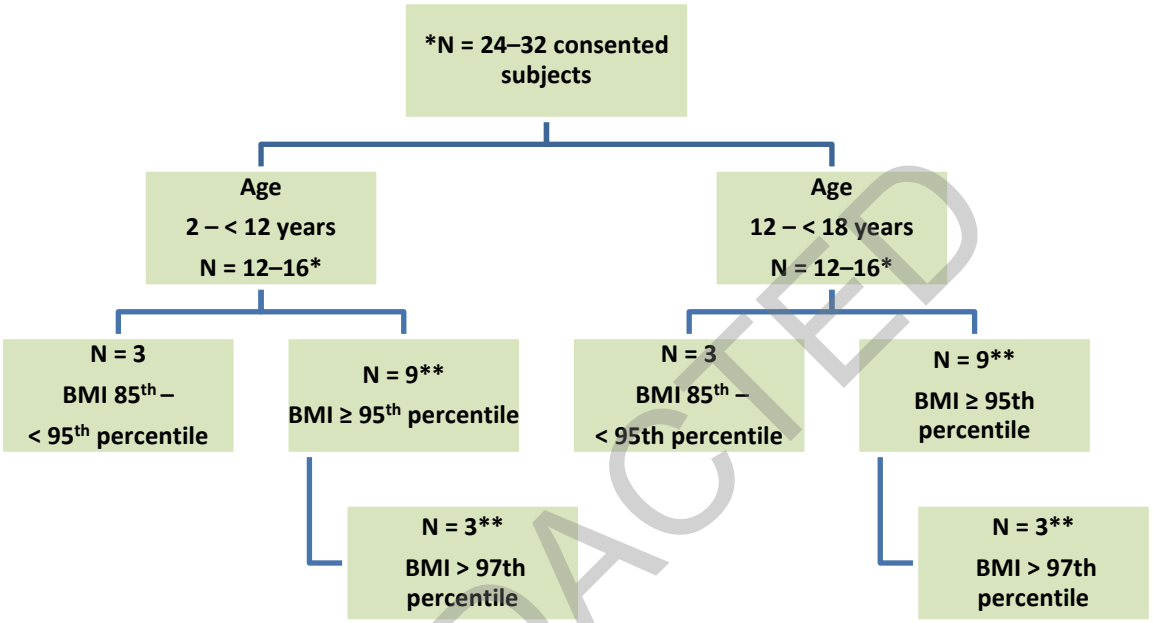
Exclusion Criteria:	1) The following apply only to those who are NOT already receiving clindamycin per routine care: a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin b. History of *C. difficile* colitis with previous administration of clindamycin c. AST >120 units/L d. ALT >210 units/L e. Total bilirubin >3 mg/dL f. Serum creatinine >2 mg/dL g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II.B**) 2) Previous participation in the study 3) Current exposure to medication listed in **Appendix II.A** 4) Participant is receiving extracorporeal life support (ECLS) 5) Participant is post-cardiac bypass (within 24 hours) 6) Participant on inotropes/pressors 7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

Table 1. Study Event Table

Study event/day	Screening/ study day 0	Study day 1 (any dose after the 1st dose of IV clindamycin; oral PK with 4th dose or later)	Study day 2–14	End of therapy (day 14) OR early withdrawal or discontinuation	3-Day post-treatment phone follow-up
Informed consent/ assent & HIPAA	X				
Medical history	X				
Demographics	X				
Concomitant medications of interest	X	X	X	X	X
Infection history	X	X			
Physical examination	X			X	
Weight	X				
Height	X				
BMI	X				
Waist:hip ratio	X				
Laboratory evaluation[a]	X			X	
α-1 glycoprotein (will be done by OpAns at their lab)[b]	X				
Laboratory evaluation (**6.6.1 Table 2**—if obtained as part of routine care)		X	X		X
Serum pregnancy test (female only)	X				
Feeding status (during PO PK portion only)		X			
Discarded scavenged samples[c]		X	X	X	
Clindamycin IV or PO[d]	X	X	X[f]		
PK samples[e]		X			
AE/SAE	X	X	X	X	X

[a]Hemoglobin, hematocrit, platelets, white blood cells, sodium, potassium, chloride, bicarbonate, total calcium, glucose, creatinine, blood urea nitrogen, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin.
[b]Central laboratory will measure this from plasma sample collected per PK schedule.
[c]Discarded blood cells may be collected at any time during the study.
[d]Group assignment (see **Figure 1**).
[e]PK sampling (**Table 3**, see **Section 6.6.2**).
[f]IV clindamycin will be continued per treating physician; when switched to PO, participant will also participate in PO PK study.

Figure 1. Schematic/Description of Study Design



*IV participants who transition to oral clindamycin will also participate in the oral PK study.
**Minimum of 3 participants with BMI > 97th percentile in each age group.

1 KEY ROLES

For questions regarding this protocol, contact:

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Over the past decade, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a leading cause of hospitalization for children and adolescents in the United States (1). Consequently, the use of antimicrobial agents active against MRSA has become more prevalent (2). Specifically, the use of clindamycin among children hospitalized with *Staphylococcus aureus* infections increased from 21% in 1999 to 63% in 2008. At the same time, rates of childhood obesity have continued to remain high. Recent national data demonstrate that 17% of children aged 2–19 years in the United States are obese (body mass index [BMI] ≥ 95th percentile) and 12.3% are morbidly obese (BMI ≥ 97th percentile) (3). Obese patients have a greater likelihood of complications from infectious diseases and are at increased risk of developing *Staphylococcus aureus* infections. Therefore, an understanding of the PK of clindamycin in this population is critical to ensure appropriate interventional therapy.

Clindamycin, a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin (4), is approved by the U.S. Food and Drug Administration (FDA) for the treatment of pediatric and adult patients with respiratory tract, female pelvis and genital tract, and skin and soft tissue infections with susceptible bacteria including streptococci, pneumococci, and staphylococci. Clindamycin is also approved in adults for septicemia and intra-abdominal and serious infections with susceptible anaerobic bacteria (5).

Clindamycin is approximately 90% protein-bound. It is metabolized by the liver and excreted via the liver, bile, and kidneys. Impaired renal function modestly decreases the elimination of clindamycin; however, dosage adjustment is not required with renal dysfunction (4). Clindamycin phosphate (intravenous [IV] formulation) is rapidly converted to active clindamycin which has an elimination half-life of about 3 hours in adults and 2.5 hours in children (5). The drug penetrates well into all tissues, with the exception of the brain and cerebral spinal fluid. It is actively taken up and concentrated within the phagocytic cells. Clindamycin binds to the 50S subunit on the bacterial ribosome and inhibits protein synthesis by interfering with the formation of initiation complexes, thus inhibiting exotoxin production (4). Clindamycin exhibits time-dependent killing; and efficacy is correlated with the time clindamycin concentrations exceed the minimum inhibitory concentration of the pathogen of interest. A summary of clindamycin serum concentrations in non-obese children is found in **Appendix IV**.

Variability in serum and tissue concentrations has been reported in obese patients (4). The underlying premise is that this is due to physiologic changes that alter a drug's volume of distribution (Vd) and body clearance (Cl) (6,7). Thus, obese patients may be dosed inappropriately if fixed or "adult" doses are used (under-dosed) or if weight-based dosing is used (over-dosed) (6,7). Because critically ill obese patients with infections are reported to have a worse outcome than non-obese patients (8), it is imperative to determine if the disposition of and response to clindamycin may be altered compared to healthy children with an infection. In addition, sub-therapeutic drug concentrations may increase the development of resistant organisms. Thus, it is important to perform pharmacokinetic (PK) and pharmacodynamic (PD)

studies in the obese pediatric population to ensure that these patients are being optimally dosed with medications designed to treat infections. There are no currently available PK (or PD) data to guide clindamycin dosing in obese pediatric or adult patients. This proposal will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years.

2.2 Scientific Rationale

Selection of the correct drug dose and dose regimen is the most important decision in ensuring optimal pharmacotherapy. Defining an optimal regimen requires a clear understanding of the drug's PK, PD, and, for many compounds, pharmacogenomic (PG) profiles. Understanding these characteristics for drugs used in pediatrics is imperative to determine optimal dose regimens across the pediatric age continuum.

Clinically, drug dosing in pediatrics is individualized to age by basing the drug dose on a patient's body weight and the dose interval on the functional capacity of the drug's clearance pathways. This approach assumes, though inaccurately, that a drug's Vd and body Cl are directly proportional to a patient's body weight. Despite this lack of proportionality, the majority of pediatric patients favorably respond to weight-based drug dosing. However, as the potency of newer drugs increases and the need for more precise drug dose regimens expands, better-defined dose regimens based on careful assessment of the drugs' integrated PK-PD-PG profiles across the pediatric age continuum are needed (9). Complicating this paradigm are the substantially increasing numbers of children and adolescents who are obese, and even morbidly obese, and the lack of data on disposition in the obese population. Clinical trials of new drugs focused on FDA labeling exclude obese patients, leaving the determination of dosing regimens in the obese for post-marketing, often investigator-initiated studies.

Antibiotic Dosing Regimens Based on PK-PD Modeling
Prior to our understanding of the integrated PK-PD characteristics for antibiotic drugs, antibiotic dosing regimens were mostly based on perceived maximum tolerated doses often related in some manner to the target pathogen minimum inhibitory concentration (MIC). Integration of an antibiotic's PK with PD allows for the determination of the optimal dose regimen across the spectrum of antibiotic drugs (10,11). In addition, this more quantitative approach permits comparisons of different antibiotic drugs for a specific infection and far more accurate predictability of patient response. The specific antibiotic PK-PD characteristic used to predict outcome (i.e., bacteriologic eradication) appears to be mostly dependent on whether the drug's bacterial killing is concentration- or time-dependent. Clindamycin is most often described as a "time-dependent antibiotic with moderate persistent effects," and as such, the best predictor of bacterial killing appears to be the ratio of the area under the clindamycin (free, unbound) drug concentration time curve (AUC) divided by the targeted pathogen MIC (i.e., fAUC/MIC) (11). To accurately determine this pivotal PK-PD parameter, what is needed is a comprehensive understanding of the drug's PK profile across the age spectrum while incorporating the spectrum of pathophysiologic changes and differing body habitus. For clindamycin, these data are not available.

Clindamycin Pharmacokinetics
Limited published clindamycin PK data exist and encompass < 100 neonates, infants, and children. In neonates, clindamycin elimination is delayed compared with older infants and children—mean elimination half-life (t ½) values of 8.7 vs. 3.6 hours, respectively (12,13). Regardless of age group studied, variability was observed in clindamycin t ½, Vd, AND systemic

Cl. In addition, some studies report variable serum clindamycin concentrations (bioactivity) following parenteral dosing (12,14). Despite this variation in drug disposition, which is observed in both children and adults, bioactive serum clindamycin concentrations remain therapeutic following routine parenteral (intramuscular, IV) or oral dosing. Considering that clindamycin, an antibiotic, is used to treat infections caused by susceptible pathogens responsible for infectious diseases regardless of patient age, pediatric clindamycin development strategies need only focus on the drug's safety and PK profile to ensure similar systemic exposure. Available clindamycin PK data support close similarity for clindamycin systemic exposure (i.e., bioactive serum clindamycin concentrations and AUC) in older infants, children, and adults following comparable mg/kg doses (12, 14–19). As noted above, clindamycin PK in premature and full-term infants is, as expected, different than that observed in older patients (12,13). This foundation of data underscores the importance of studying clindamycin disposition in the obese pediatric patient.

Clindamycin is extensively bound to plasma protein, primarily to alpha 1 acid glycoprotein, and, with the exception of the brain or cerebrospinal fluid, effectively penetrates body tissues and fluids. The drug is metabolized primarily by the cytochrome (CYP) P450 isoenzyme CYP3A4 to two primary, antimicrobial active metabolites, a sulfoxide and to a lesser extent N-demethylclindamycin (20). Although only limited data are available for current clindamycin pediatric dosing regimens, the regimens employed clinically have been used for decades with apparent success. Nevertheless, clindamycin optimal dosing regimens in pediatrics remain unknown. Furthermore, the influence of obesity on clindamycin disposition is unknown and may have a far greater negative impact on patient outcome due to ill-defined, clinically extrapolated dosing.

Drug Dosing and Obesity

Data defining optimal drug dosing in the obese and morbidly obese adult patient are very limited and virtually non-existent in pediatrics. Drug dosing on total body weight (TBW) in the obese patient has the real risk of overdosing the patient, resulting in an increased incidence of adverse effects, while dosing on ideal body weight (IBW) can lead to serious under-dosing. In obese adults, IBW is increased by 20–40%, which is unaccounted for when using the many mathematical formulas available to calculate dosing based on a person's IBW. This deficiency may partially explain the inaccuracy of drug dose regimens for obese patients based on IBW formula estimations (21–26).

The influence varying degrees of obesity have on important physiologic functions across the age continuum in pediatrics is unknown. In adults, sparse data suggest that obese adults may have altered tissue blood flow rates due to inherent differences in blood flow to lean (greatest amount) and adipose tissue, impaired cardiac function, and alterations in phase I and II metabolism. Although intuitive, one might assume that a drug's Vd would be increased in obese patients for lipophilic compounds, though in fact, for the few drugs assessed, the Vd is highly variable. Similarly, Cl is also highly variable in the obese population, underscoring the need to determine drug disposition characteristics not only across the age continuum but also with increasing degrees of obesity (21–24). No such data are available for the pediatric patient, but these data combined underscore the need to critically assess a drug's disposition relative to age and body habitus. Furthermore, for antibiotics whose efficacy is dependent on achieving effective concentrations at the infectious site, interfaced with the organism, optimal dosing in the obese pediatric patient must be defined (6,7).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of Blood Draws
There are small risks to blood sampling, usually some pain/discomfort with the blood stick. Every effort will be made to avoid additional (to standard of care) sticks for this study by timing clinical blood draws to coincide with timed samples when possible and the use of existing IV lines when feasible for the blood draws.

Risks of Clindamycin
From the FDA label and review of the literature, the following are adverse reactions of clindamycin: antibiotic-associated colitis, pseudomembranous colitis, abdominal pain, nausea, and vomiting; hypersensitivity reactions (maculopapular rash and urticaria have been observed during drug therapy; generalized mild-to-moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions; rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin; a few cases of anaphylactoid reactions have been reported). Organ systems that are affected include skin and mucous membranes (pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported); liver (jaundice and abnormalities in liver function tests have been observed during clindamycin therapy); renal system (although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances); hematopoietic (transient neutropenia [leukopenia] and eosinophilia have been reported; reports of agranulocytosis and thrombocytopenia have been made; no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances); local reactions (pain, induration, and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion); musculoskeletal (rare instances of polyarthritis have been reported); cardiovascular (rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV administration). There is minimal additional risk to the participants who are receiving clindamycin as part of their routine medical care.

2.3.2 Known Potential Benefits

The participant may benefit from the use of the study drug; however, participation in this study has no other potential benefits to the participants. The results of this study may benefit overweight and obese participants in the future who require clindamycin therapy.

3 OBJECTIVES

Primary Aim
Characterize the PK of multiple-dose IV clindamycin in overweight and obese children and adolescents.

Secondary Aims
1. Characterize the PK of multiple-dose oral clindamycin in overweight and obese children and adolescents.
2. Characterize the safety profile of clindamycin in overweight and obese children and adolescents.

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1. PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUC_{tau})

3.1.2 Secondary Outcome Measures

1. PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2. Safety profile: Adverse events will be collected during and after study drug administration.

4 STUDY DESIGN

This will be a prospective, open-label PK and safety profile study of multiple doses of IV and oral clindamycin in overweight and obese children 2 – < 18 years of age. The total study duration is expected to be approximately 24 months; each participant will participate in the study for up to 18 days (screening day; treatment days 1–14 [may be as short as 2 days] followed by an observation period of 3 days post discontinuation of clindamycin therapy or after day 17 [on day 18] of therapy in those who are treated with more than 14 days of clindamycin).

5 Study Population

Selection of the Study Population

Eligible participants ages 2 – <18 years will be identified through the inpatient units at each participating site. There will be up to 32 evaluable participants (defined in **Section 10.3**) enrolled; however, target enrollment will be 24 participants. If dosing changes are suggested by the interim PK analysis (see **Section 10.3**), approximately 8 additional participants will be enrolled. Twelve to 16 participants will be enrolled in each of the following age groups: 2 – < 12 years and 12 – < 18 years of age. Participants will be further stratified into 1 of 2 groups based on their BMI (85th – <95th percentile, and ≥95th percentile). No more than 3 participants with BMI in the 85th – <95th percentile will be enrolled in each age group. Participating sites will prioritize enrollment of participants with BMI >97th percentile in each age group.

5.1 Inclusion/Exclusion Criteria

The investigator or other study site personnel will document in the source documents (e.g., the hospital chart) that informed consent and assent (if applicable) were obtained. Laboratory tests or non-pharmacologic treatment procedures that were performed and considered "routine care" within 72 hours of first dose of study drug may be used for screening procedures required by the protocol and recorded in the case report form (CRF).

Inclusion Criteria

1) 2 years – < 18 years of age at the time of first dose of study drug
2) Suspected or confirmed infection OR receiving IV clindamycin per routine care
3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours of first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug
4) BMI ≥ 85th percentile for age and sex, based on CDC recommendations
5) Signed informed consent/HIPAA documents by the parent/legal guardian and assent (if applicable)

Exclusion Criteria

1) The following apply only to those who are NOT already receiving clindamycin per routine care:
   a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin
   b. History of *C. difficile* colitis with previous administration of clindamycin
   c. AST > 120 units/L
   d. ALT > 210 units/L
   e. Total bilirubin > 3 mg/dL
   f. Serum creatinine > 2 mg/dL
   g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II.B**)
2) Previous participation in the study
3) Current exposure to medication listed in **Appendix II.A**
4) Participant is receiving extracorporeal life support (ECLS)
5) Participant is post-cardiac bypass (within 24 hours)

6) Participant on inotropes/pressors
7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

5.2 Treatment Assignment Procedures

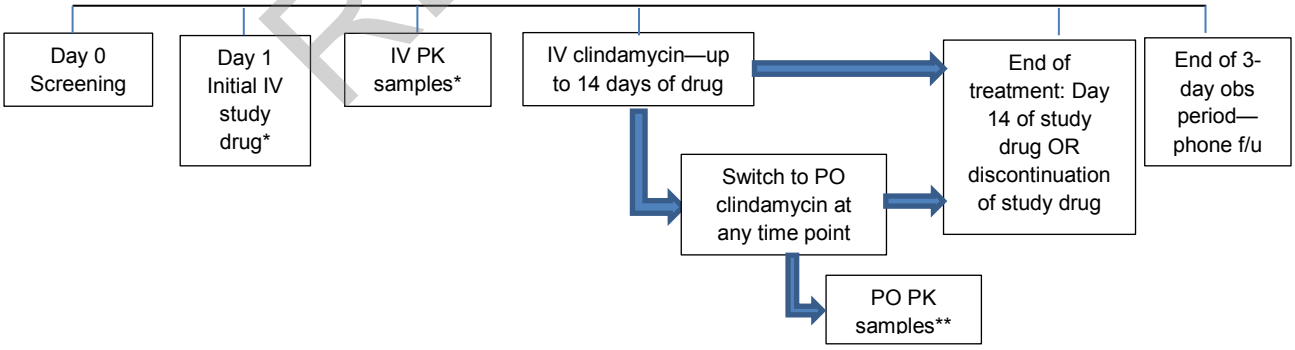
This will be an open-label PK study. Participants will be assigned to age groups based on age upon first dose of study drug and to a BMI group based on BMI at study entry.

5.2.1 Duration of Study Participation

Duration of therapy will be up to 14 days for children who receive the first dose of clindamycin as the study drug. All participants will begin on IV therapy and must receive at least 2 doses of IV clindamycin to participate in the study. The total duration of therapy with clindamycin will be determined by the treating physician for those children who are receiving clindamycin as part of routine care; however, only 14 days of therapy from the time of enrollment will be considered as study drug. Study follow-up will occur 3 days (+/- 1 day) after the last dose of study drug. Patients who are receiving antimicrobial agents other than clindamycin may enroll in this study and receive up to 3 doses of IV clindamycin and 4 doses of oral clindamycin in addition to their standard of care therapy. Participants who transition to oral clindamycin may return as outpatients to complete the PK portion of the study.

Total duration of study participation will be up to 18 days. This will comprise a 1-day screening period; a maximum 14-day treatment period; and a 3-day post-study observation period to monitor for serious adverse events. The 3-day post-treatment visit may be a phone follow-up. Patients may continue clindamycin per their physician's recommendation after they have completed participation in this (maximum of) 18-day study.

Figure 2.Timeline



*Minimum of 1 doses of IV clindamycin before IV PK period.
**Minimum of 3 doses of PO clindamycin before PO PK period.

5.2.2 Replacement Participants

Participants in the IV portion of this study who are unable to provide at least 3 timed PK samples may be replaced.

5.2.3 Reasons for Participant Withdrawal

A participant or his/her parent/guardian may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the participant from participating in this study at any time. Participants may be prematurely discontinued from the study for any of the following reasons:

- Participant or investigator noncompliance with the study protocol
- At the request of the participant, investigator, treating physician, or sponsor
- Adverse reaction or suspected adverse reaction.

Participants are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. The participant who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations, and will be provided appropriate care under medical supervision until the symptoms of any adverse event (AE) resolve or the participant's condition becomes stable. Participants withdrawn from the study due to an AE must be followed per protocol (see **Section 8.2.4**).

5.2.4 Termination of Study

This study may be terminated at any time by NICHD, the Investigational New Drug Application (IND) sponsor, or the Data Monitoring Committee (DMC) if serious adverse reactions occur in 2 or more participants that are directly related to study drug, or if, in NICHD's judgment, there are no further benefits to be achieved from the study. A study site may be terminated if the investigator does not adhere to the study protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

See the schedule of study events and procedures (**Table 1**).

1. Medical history will be obtained by interview with the parent/legal guardian/participant and from the participant's medical records.

2. Concomitant medications of interest administered within 7 days prior to first study dose and during the period of administration of study drug, including herbal products of interest, will be recorded (see **Appendix II**).

3. Physical examination, including abnormal physical findings, height (measured standing if possible), weight and waist:hip ratio will be obtained. NOTE: The initial physical examination information (except the height, weight, and waist/hip measurements) may be obtained from the medical record but must have been performed within 24 hours prior to enrollment. BMI will be calculated from height and weight using the following formula: BMI = [weight (kg) / (stature (cm))^2] x 10,000. Refer to the Centers for Disease Control (CDC) pediatric BMI calculator (http://apps.nccd.cdc.gov/dnpabmi/) to determine the BMI. The BMI percentile will be obtained using the BMI calculator and verified using the age- and sex-specific CDC BMI charts (**Appendix I**).

4. The safety laboratory testing will be performed at each site's local laboratory. Baseline laboratory values may be used if obtained as part of routine care within 72 hours prior to study enrollment. The serum pregnancy test will also be performed at the local laboratory (within 24 hours prior to study enrollment). Alpha-1-glycoprotein will be measured by OpAns at their laboratory using plasma already collected as part of the PK sample collection.

5. PK sampling (see **Section 6.6.2**).

6.2 Screening

Research staff at sites will screen potential participants for eligibility requirements per local institutional policies.

6.3 Enrollment/Baseline

Baseline/Pre-Dose Assessment (Day 0)
After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA documents, the participant has signed assent (if applicable), and after it has been determined that the participant satisfies all inclusion and no exclusion criteria, the following evaluations will be performed and recorded in the CRF:

1. Participant demographics
2. Physical examination, including weight, height, waist:hip ratio, and BMI
3. Pertinent medical history
4. Concomitant medications of interest (7 days prior to first dose of study drug) (see **Appendix II**)
5. Laboratory determinations (see **Table 2**, **Section 6.6.1**)
6. Culture results of blood, urine, sputum, or wound (if obtained as part of routine care) within 72 hours prior to the first dose of study drug
7. For participants receiving clindamycin per routine care, the date and time for the doses administered prior to first dose of study drug will be recorded (up to a maximum of 6 prior doses)
8. Serum pregnancy test (females only who have reached menarche) within 24 hours of study enrollment

Assessments/Procedures (Days 1–14)
The participant will start study drug upon completion of the pre-assessment, or, if s/he was already receiving clindamycin (at the study-recommended dose), s/he will continue receiving that dose of clindamycin. If s/he was receiving clindamycin at a dose lower than the study-recommended dose, the dose will be changed to be in compliance with the protocol. Total body weight will be used to calculate the absolute dose administered. Refer to **Section 7.1.2** for dosing. Participants who transition to oral therapy will also participate in the oral-dose PK portion.

The following assessments will be conducted after the participant receives the first dose of clindamycin after study enrollment and throughout therapy up to day 14:

1. Concomitant medications of interest (see **Appendix II**)
2. Start date/time and stop date/time of clindamycin administration and flush date/stop time after IV administration
3. Feeding status (during PO PK portion only): nothing by mouth (NPO), clear liquids, full feeds, etc.
4. Collection of PK samples (including date/time) (see **Section 6.6.2**)
5. Results for laboratory tests of interest (see **Section 6.6.1**)
6. Collection of culture results (if available)
7. Adverse events (see **Section 8.2.1**)

6.4 End of Therapy OR Early Withdrawal/Discontinuation

The following assessments will be conducted at early withdrawal or end of therapy:

1. Concomitant medications of interest (see **Appendix II**)
2. Physical examination
3. Laboratory evaluations (see **Section 6.6.1**)
4. Adverse events (see **Section 8.2.1**)

6.5 Follow-up Safety Phone Call

Assessments/Procedures (Day 3 Post Treatment): This visit will be a phone follow-up unless the participant is still hospitalized. This assessment will occur 3 days (+/- 1 day) after the last dose of study drug. The following information will be obtained:

1. Adverse events (see **Section 8.2.1**)
2. Concomitant medications of interest (**Appendix II**)
3. Any labs collected

6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

Laboratory testing (**Table 2**) will be collected on all participants and be performed in the local laboratory at each site. Laboratory values will be collected within 72 hours prior to enrollment. Laboratory values performed as part of routine care within 72 hours prior to enrollment may be used for baseline laboratory tests. Laboratory values will also be obtained at the end of therapy. Laboratory values obtained within ± 24 hours of discontinuation of study drug or within ± 24 hours of completion of 14 days of study drug (if they are continuing clindamycin beyond 14 days) may be used as end-of-treatment laboratory values. If these laboratory tests have not been performed as part of routine care, they will be performed for the study per the protocol schedule. The serum pregnancy test will also be performed at the local laboratory. Alpha (α)-1-glycoprotein will be measured from one of the PK samples by the central laboratory once during the study using an ELISA kit (central laboratory). Sites do not need to collect an extra sample to measure α-1-glycoprotein.

Table 2. Laboratory Evaluations

Hematology	Serum Biochemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Platelets	Chloride
White blood cells	Bicarbonate
	Total calcium
	Glucose
	Creatinine
	Blood urea nitrogen
	Total protein
	Albumin
	Aspartate aminotransferase
	Alanine aminotransferase
	Bilirubin

6.6.2 Special Assays or Procedures

PK Samples
Blood (0.5 mL) will be collected with scheduled IV and oral doses of clindamycin for clindamycin plasma concentration determinations (see **Table 3** below for schedule). In participants receiving IV clindamycin, PK samples should be collected from a site separate from the site of administration. PK samples in participants on IV clindamycin will be collected with any dose after the first dose of study drug (excluding the first dose), and, for PO clindamycin, PK samples with any dose after the 3rd dose of study drug (excluding the 3rd dose). The PK sampling will be drawn according to the following schedule relative to the end of infusion (IV PK) or actual time of oral administration (PO PK).

Table 3. PK Schedule

Scheduled PK Sampling Times				
Time (hours)*	**IV dose***		**PO dose**	
	Q6h	**Q8h**	**Q6h**	**Q8h**
Pre-dose 0 (within 15 minutes prior to the dose)	**X****	**X****	**X****	**X****
0.5 (± 5 minutes)	**X****	**X****	N/A	N/A
1–1.5	X	X	**X****	X**
3–4	**X****	**X****	**X****	--
5–6	--	X	--	**X****
Pre-dose (will depend if on q6h or q8h dose schedule)	**X****	**X****	**X****	**X****
Total number of samples	5	6	4	4

* Time starts at end of flush after the 30-minute infusion.
** Priority samples (see paragraph below).

Every effort should be made to collect all PK samples for each participant. Collection of PK samples should be timed with collection of laboratory tests per standard of care to minimize blood draws specifically for the study. If it is impractical to collect all PK samples during the same dosing interval, samples can be obtained at different dosing intervals. If it is impossible to obtain all PK samples for each participant, **PK samples can be prioritized to include:**

a) **For IV administration: pre-dose, 0.5 hours, 3–4 hours, and pre-next dose**
b) **For oral administration: pre-dose, 1–1.5 hours, 3–4 hours (q6h dosing), 5–6 hours (q8h dosing), and pre-next dose**

Clindamycin concentrations in plasma will be measured at a central laboratory using a validated bioanalytical assay. In addition, scavenged samples will be obtained.

Scavenged Plasma Sampling
Plasma samples collected in EDTA tubes during the course of therapy (~100 µL plasma or ~200 µL whole blood) will be procured, after consent. A maximum of 10 scavenged plasma samples will be collected per participant. Collection may begin with any specimen collected after the first dose of study drug through 24 hours after the last dose of study drug. The date and time of

sample collection, as well as the date and time the sample is frozen, will be collected for all scavenged samples.

Minimizing Blood Loss
To minimize the amount of blood sampling, laboratory values will be obtained only at baseline and end of study. If they have been obtained as part of routine care within 72 hours prior to enrollment into the study, the baseline laboratory values do not need to be repeated. The PK sampling scheme will be employed such that no more than a total of 8 mL (< 3 mL/kg) of blood is obtained from each participant for PK analysis. Plasma samples will be collected in 0.5 mL blood aliquots.

6.6.3 Specimen Preparation, Handling, Storage, and Shipping

Detailed information for collection, labeling, preparation, handling, storage, and shipping of specimens is detailed in the manual of procedures (MOP).

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

A dose of 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 g/day is selected based on current labeling. Patients who are receiving clindamycin as part of their routine care are also eligible to participate if their dose can be adjusted to be at least 30 mg/kg/day upon enrollment. The dose administered will be based on TBW. Because bioavailability is estimated at 85%, the same dose will be used for oral administration as is used for IV dosing. Both solution and capsule preparations will be included in this study because both oral formulations are used in clinical practice, and it will allow the inclusion of those patients who cannot swallow pills. In the absence of PK data, we assume that drug clearance will be comparable in obese pediatric patients compared to non-obese pediatric patients. Therefore, a dosing regimen 30–40 mg/kg per day and a maximum dose of 2.7 g/day should provide exposures similar to those used in children and adolescents with a normal BMI. It is predicted to be safe in the obese population because similar doses are currently used per routine care.

7.1.2 Dose and Timing

Both q6h and q8h dosing will be allowed for both oral and IV dosing of clindamycin. For children receiving clindamycin as part of clinical care, this protocol will not prescribe a route of administration or dosing interval; the dose, route of administration, and dosing interval prescribed by the treating physician will be recorded on the CRF. Dosing greater than 2.7 g/day will be allowed for children receiving clindamycin as part of clinical care. However, if the prescribed dose is less than the lowest dose for this study, the dose of clindamycin will be changed to comply with the study-recommended dose. See **Section 5.2.1** for duration of therapy.

IV dosing: A minimum of 2 doses of IV clindamycin will be administered. The dose administered will be based on TBW at 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 grams/day. The drug will be administered over 30 (+/– 5) minutes. The venous access line will be flushed per local practice after completion of IV administration, and the time of the end of flush will be documented. It is preferred that the flush be ≤1 minute after the end of infusion.

Oral dosing: For those participants who are receiving clindamycin as a solution, they will receive 30–40 mg/kg/day divided q6h or q8h. For those participants receiving the capsule formulation, they will receive the dose of clindamycin defined in **Appendix III**. Only whole capsules will be used. The oral solution will be used for those participants who cannot swallow capsules. No more than 12 PO study drug doses will be administered as part of this study.

7.1.3 Formulation, Packaging, and Labeling

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules.

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles for reconstitution.

Each formulation is approved for use in the United States.

7.1.4 Product Storage and Stability

Clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules), and clindamycin palmitate (PO oral solution) will all be stored at room temperature (20–25^0 C). Diluted clindamycin phosphate (IV) is stable at room temperature for at least 16 days and refrigerated for at least 32 days. Reconstituted clindamycin palmitate hydrochloride, USP for oral solution is stable for 2 weeks at room temperature and should not be refrigerated. See the MOP for detailed information.

7.2 Preparation and Administration of Study Intervention/Study Drug

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL. The drug will be infused over 30 (+/– 5) minutes. Infusion rates should not exceed 30 mg/minute. The pharmacy will prepare the IV formulation, and the dose administered will be based on TBW.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules, and the dose will be dispensed based on TBW (see **Appendix III** for dosing).

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles and will be prepared in the pharmacy at each site based on the reconstitution recommendation in the label. The dose administered will be based on TBW.

Refer to the MOP for additional details regarding drug procurement, drug preparation, and administration.

7.3 Modification of Study Intervention/Investigational Product for a Participant

No dosing adjustments are required for hepatic or renal impairment.

7.4 Accountability Procedures for the Study Intervention/Study Drugs

Each site will provide drug for their study participants. The study product accountability records will be maintained in the pharmacy study binder for clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules) and clindamycin palmitate (PO oral solution). See MOP for specific details related to investigational product accountability.

7.5 Assessment of Participant Compliance w/ Study Intervention

Compliance with dosing will be determined using the pharmacy accountability logs and the participant's medication administration record. For those participants who are discharged on oral clindamycin and have not completed the PO PK visit, the participant or parent/guardian will keep a drug administration diary and all drugs will be accounted for at the outpatient PK study visit.

7.6 Concomitant Medications of Interest/Treatments

Concomitant medications of interest are listed in **Appendix II**. Children who are prescribed one of these medications after enrollment may continue in the study.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

AEs will be collected during and after study drug administration and for 3 days following end of therapy with clindamycin. Results will be tabulated by MedDRA System Organ Class and Preferred Term.

8.2 Methods & Timing for Assessing, Recording, & Analyzing Safety Parameters

AEs will be collected from the time of consent, throughout the period of study drug administration, and for 3 days following end of therapy with clindamycin. See **Section 8.6** for clarification for AEs identified at the 3-day follow-up visit and for serious AEs (SAEs). Safety will be assessed by frequency and incidence of AEs and SAEs. The Best Pharmaceuticals for Children Act (BPCA) safety monitoring committee (DMC) convened by NICHD will review data and safety information from study participants.

8.2.1 Adverse Event

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

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

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

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

1. Death
2. Life-threatening AE (“life-threatening” means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.2.2 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, investigational plan, or informed consent.

8.2.3 Identification of Events and Timeframe for Reporting

As all participants in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after consent has been obtained. The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome. Any event beginning more than 3 days after the last dose of study drug will not be captured.

8.2.4 Follow-up of Adverse Events

AEs ongoing at the time of the last dose of study drug will be followed up to 3 days after the last dose of study drug. AEs that resolve during the study or follow-up period will have the resolution date documented in the CRF. Adverse events that are identified at the last assessment visit/phone contact (or at the early termination visit) must be recorded on the AE CRF, with the status of the AE noted. Any events that are identified at the last assessment visit/phone contact will be followed for an additional 3 days for AEs and 10 days for SAEs and if still ongoing can be “resolved by convention”. All serious suspected adverse reactions will be followed until resolution. All enrolled participants in both cohorts who receive at least 1 dose of clindamycin will be followed for safety.

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. **MODERATE**: Participant experiences enough symptoms or findings to require intervention
3. **SEVERE**: Participant experiences symptoms or findings that require significant intervention

8.4 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction. ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.5 Reporting Procedures and Timeframe for Reporting

All AEs will be entered into the data system within 72 business hours of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties encountered when entering the event into the electronic data capture (EDC) system, the SAE will be reported to the data coordinating center (DCC) by telephone or FAX communication. Investigators must submit safety reports as required by their local IRB, independent of the reporting requirements specified in the protocol.

8.5.1 Serious Adverse Events

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC, IND sponsor, protocol chair, and funding sponsor (NICHD). The BPCA DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.5.2 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The sponsor or his representative will submit expedited safety reports (IND safety reports) to the FDA and other regulatory agencies as necessary, and will inform the DMC and investigators of such regulatory reports. Site investigators must submit IND safety reports as required by their IRB. Documentation of the submission to and receipt by the IRB should be retained for each IND safety report. The sponsor will submit a progress report of the investigation annually, which will include a summary showing the most frequent and most serious adverse events by body system.

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

Adverse events will be followed by the investigator or a clinician member of the study team in person if the participant is hospitalized for an AE or SAE. If the participant is not hospitalized, the investigator or a clinician may review the participant’s medical record, contact the participant by phone, or contact the participant’s primary care physician for follow-up.
Participants withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator. Refer to **Section 8.2.4** for follow-up of AEs/SAEs. The medical monitor or study principal investigator must be notified if the AE may relate to overdose of study treatment.

8.7 Halting Rules

Participant safety data will be reviewed on an ongoing basis to monitor for halting criteria.

The study enrollment and dosing will be halted for a safety review by the BPCA DMC if serious adverse reactions occur in ≥ 2 participants.

Furthermore, the NICHD, the IND sponsor, protocol chair, the DMC, and the investigators shall have the right to recommend termination of this study at their discretion. Possible reasons for termination of the study include, but are not limited to:

1. Adverse events
2. Unsatisfactory enrollment with respect to quantity or quality

The study may be placed on hold or terminated at a site(s) for the following reasons:

1. Inaccurate or incomplete data collection
2. Falsification of records
3. Failure to adhere to the protocol

8.8 Safety Oversight

This study will be overseen by the BPCA DMC, the NICHD, and the FDA. The DMC will review data from individual study participants on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study participants. This evaluation will also assess data quality and timeliness, participant recruitment, accrual, and retention. These reviews will allow the DMC to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DMC to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided.

Ad Hoc Meetings of the DMC: The DMC may convene an ad hoc meeting to discuss any issue of safety raised by an investigator, the IND sponsor, or a member of the DMC. At the discretion of the investigators, the sponsor, and DMC members, a non-serious AE that is 1) associated with the product and 2) does not meet the stopping rules criteria may be considered as a trigger for an ad hoc DMC meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCC or Duke Clinical Research Institute (DCRI) sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations, the DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan. Site visits will be made at standard intervals as defined by the clinical monitoring plans and may be made more frequently as directed by the IND and funding sponsors. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Study Outcome Measures

10.1.1 Primary Outcome Measures

1) PK parameters after multiple IV doses of clindamycin:
    - Clearance (Cl)
    - Volume of distribution (Vd)
    - Area under the curve (AUC_{tau})

10.1.2 Secondary Outcome Measures

1) PK results of patients transitioned to oral clindamycin:
    - Oral apparent clearance (Cl/F)
    - Oral apparent volume of distribution (V/F)

2) Safety: Adverse events will be collected during and after study drug administration.

10.2 Sample Size Considerations

It is anticipated that 12 children will be enrolled and treated in each of the IV groups for each age strata, leading to a total sample size of 24 participants. A sample size of 24 participants will provide adequate precision in the Cl/F PK parameter estimate. Assuming an inter-individual 40% coefficient of variation in the population Cl parameter estimate after weight-based allometric scaling, a sample size of 24 participants would provide a margin of error of ± 16% in the 95% confidence interval of the Cl estimate.

10.3 Analysis Plan

Population for Analysis
All participants that receive at least 1 dose of study drug will be included in the safety analysis. All participants with at least 1 evaluable PK sample will be included in the PK analysis plan. If participants have < 3 timed PK samples, additional participants may be enrolled to ensure appropriate analysis.

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

Demographics and Baseline Characteristics
The number of participants completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be summarized. Variables include race, ethnicity, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized by age and BMI cohorts.

Laboratory data, such as hematology and serum chemistry data, will be tabulated by age and BMI cohorts. Continuous laboratory measurements will be described using univariate 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.

Interim PK Analyses
An interim PK analysis of each age cohort will be performed after approximately 4 participants have been enrolled into that cohort. If an interim analysis suggests that PK data is required on more than 12 participants in that age cohort to evaluate the PK of clindamycin in this population, approximately 4 additional participants will be enrolled into that age group for a total of 16 participants.

PK Analysis
Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance. The influence of covariates (i.e., TBW, BMI, lean body weight, adjusted body weight, IBW, etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each participant. The plasma concentrations-time profiles of clindamycin will be presented in figure form by participant and cohort (age and weight/BMI). Descriptive statistics will be presented for continuous and categorical variables. A detailed description of PK/PD analyses can be found in the PK analysis plan. We will compare PK parameters in this study of obese children to non-obese children.

11 PARTICIPANT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. “Authorization” is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the participants' families. Consent forms describing in detail the study procedures and risks are given to the participant's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the participant's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant's legal guardian and answer any questions that may arise. The participant's legal guardian will sign and date the informed consent document prior to the participant being enrolled in the study. The participant's legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participant's legal guardian for their records. The rights and welfare of the participant will be protected by emphasizing to their legal guardian that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the participant's risk to receive the investigational product. This new information will be communicated by the investigator to participant's legal guardian who consented to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participant's legal guardian will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed.

By signing the informed consent form, the participant's legal guardian agrees that the participant will complete all evaluations required by the trial, unless the participant is withdrawn voluntarily or is terminated from the trial for any reason.

12.1 Assent Process (e.g., Minor)

When a study includes participants who may be enrolled in the study only with the consent of the participant's legally acceptable representative (e.g., minors), the participant should be informed about the study to the extent compatible with the participant's understanding. If capable, the participant should assent and sign and personally date the IRB-approved written assent form (if applicable based on local IRB guidelines). The assent form describes (in simplified terms) the details of the study, study procedures, and risks. Assent forms do not substitute for the consent form signed by the participant's legal guardian. Consult with the institution's policies regarding enrollment of participants who are unable to provide informed consent for themselves.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record participant data. The CRF will be used for the recording of all historical participant information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator. Data collection forms will be derived from the CRFs and provided by the DCC.

According to ICH E6, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file (regulatory binder) at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- MOP (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records

kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the principal investigator, Pediatric Trials Network, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 50, 45 CFR 46 and 21 CFR 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

15.2 Institutional Review Board

This protocol is to be reviewed in accordance with subpart D of 45 CFR 46. Prior to its implementation, this protocol, including any subsequent amendments, the informed consent form, assent form, and any materials or advertisements presented to participants, must be approved by an IRB constituted according to FDA regulations 21 CFR 56.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution’s federal-wide assurance number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Informed Consent

The investigator will choose participants in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, a participant’s parent/legal guardian will sign one informed consent for study enrollment. All participants’ parents/legal guardians must sign an informed consent form that complies with the requirements of both 21 CFR 50 and HIPAA before the participant enters the trial. A consent form that complies with the requirements of 21 CFR 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the participant’s protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see **Section 12**.

15.4 Participant Confidentiality

Participants will be assigned unique code numbers and will not be identified by name. Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Clinical study sites will permit access to such records.

15.5 Study Discontinuation

If the study is discontinued, enrolled participants will continue to be followed for safety assessments for 3 days following the last dose of study drug, unless there is an ongoing SAE for which the participant will be followed for up to 10 days after the last dose of study drug.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the CRFs and provided by the DCC to the sites to record and maintain data for each participant enrolled in the study that is not otherwise captured in the medical record. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the CRF should be consistent with the source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the source documents and CRFs.

16.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team in real time. The site data entry staff will ensure that they are accurate and complete, and should enter the data into AdvantageEDC^{SM} within 72 business hours of data acquisition. Serious adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee in real time, and entered into AdvantageEDC^{SM} within 24 hours of identification. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

16.2 Data Capture Methods

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

16.3 Types of Data

Data for this study will include demographic data, medical history, physical examination data including height/weight/BMI, safety, laboratory, and outcome measures including PK data.

16.4 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected quarterly.

16.5 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the Investigator for 10 years after the end of the study or per local/state regulations or until participants reach 21 years of age, whichever is longer. Study information in a participant's medical records will be retained forever. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the PI when documents are no longer required to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the DCC's AdvantageEDC^{SM}.

A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB per their guidelines. The site principal investigator/study staff are responsible for knowing and adhering to their IRB requirements.

16.7 Participant Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 PUBLICATION POLICY

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

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

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research.

18 LITERATURE REFERENCES

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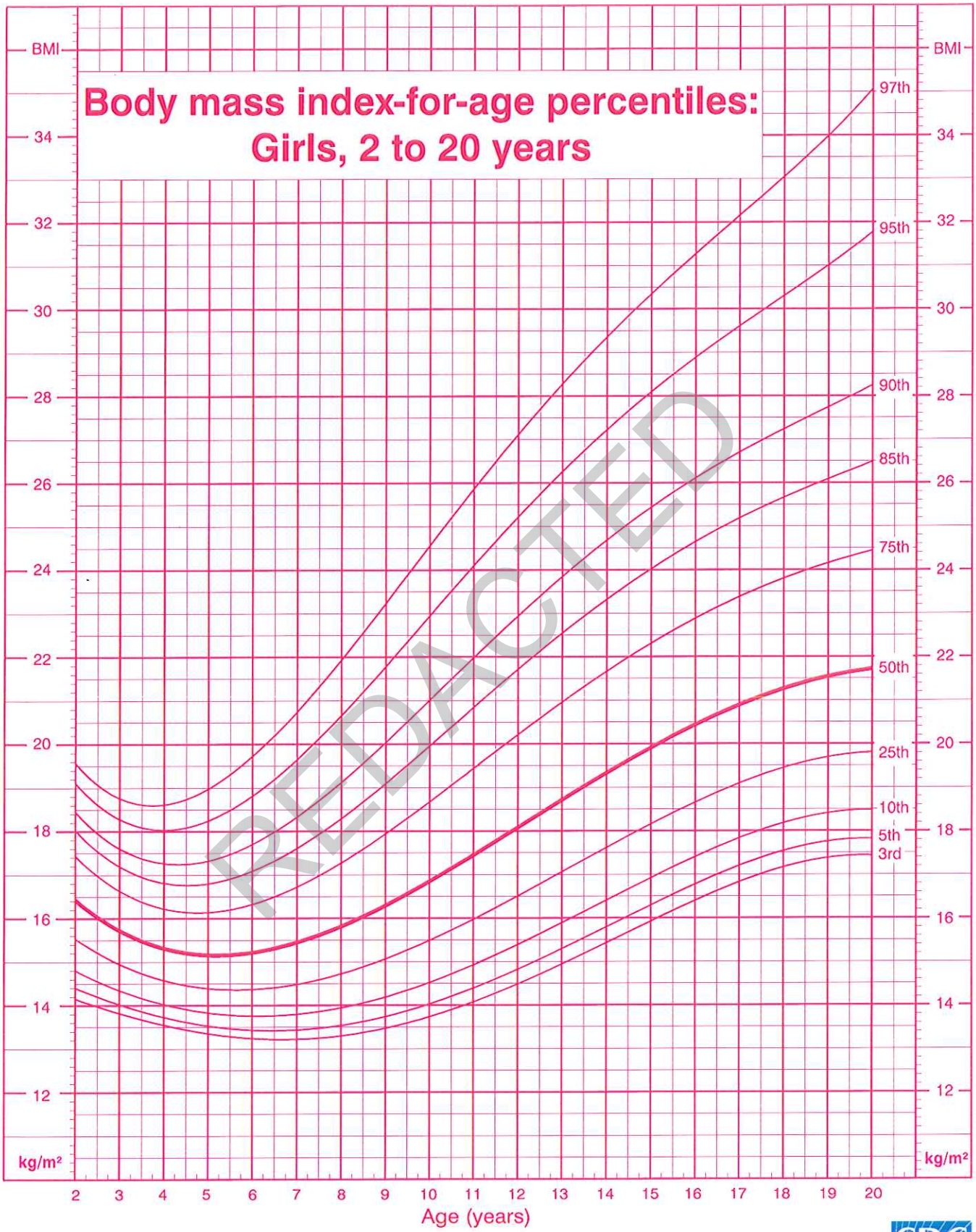
APPENDIX I

CDC Male and Female Child BMI Percentile Charts



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SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

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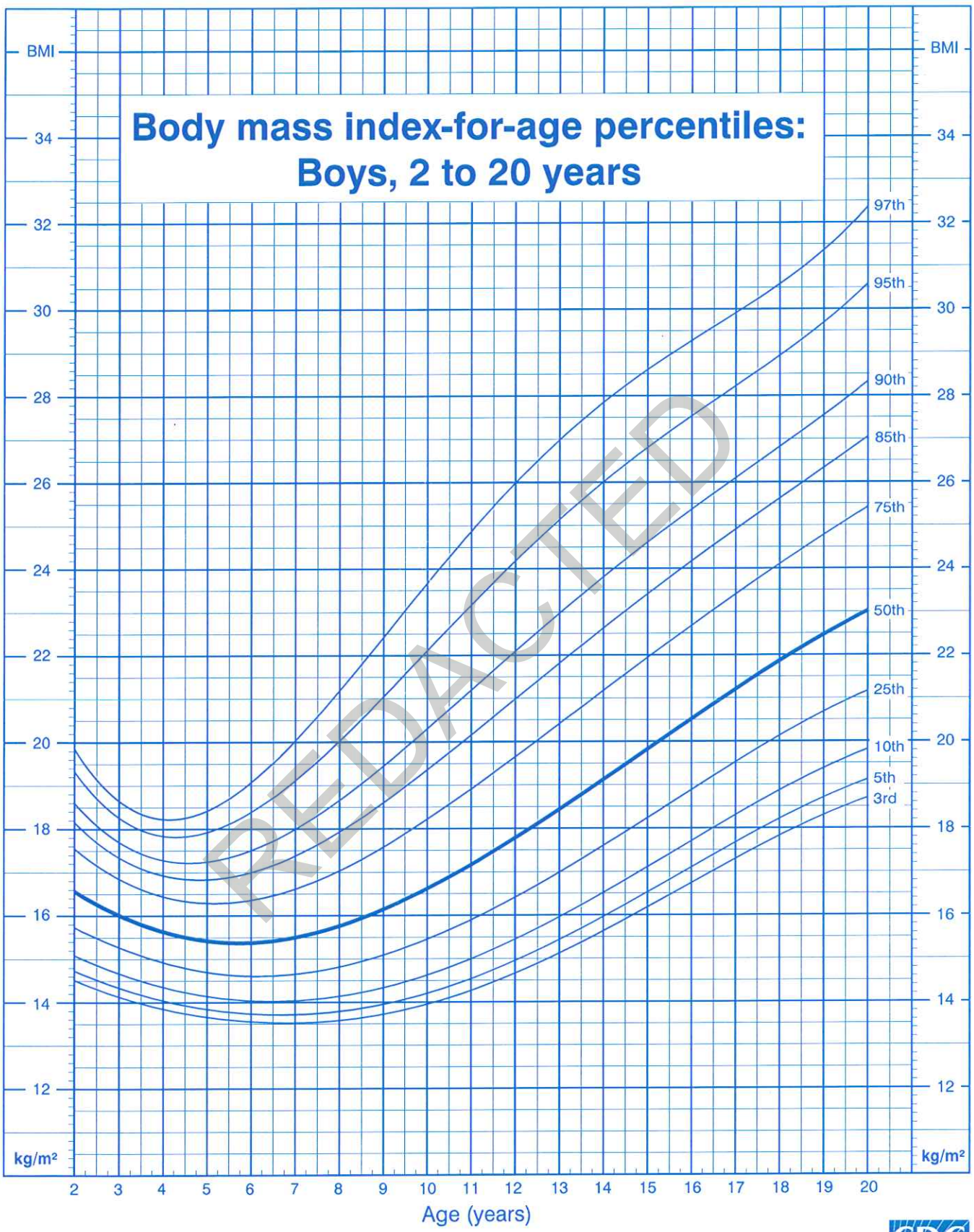

Published May 30, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion

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APPENDIX II – Medications of Interest

A. Exclusion for ALL participants at the time of enrollment:

1) CYP 3A4 potent inhibitors including:
   a. Cyclosporine
   b. Erythromycin, clarithromycin
   c. Itraconazole, ketoconazole
   d. Ritonavir, delavirdine, protease inhibitors
   e. Nefazodone, fluoxetine, fluvoxamine
   f. Verapamil and diltiazem
2) CYP 3A4 inducers
   a. Rifampin,
   b. Phenytoin
   c. Ritonavir
3) Other: St. John's Wart

B. Exclusion at the time of enrollment (unless the participant was receiving these drugs prior to enrollment AND was receiving clindamycin as part of routine care prior to enrollment):

1) Neuromuscular blocking agents: Clindamycin may enhance neuromuscular blocking effect.
   a. Atracurium
   b. Cisatracurium
   c. Pancuronium
   d. Rocuronium
   e. Succinylcholine
   f. Vecuronium

The above drugs are only excluded at the time of enrollment; if a participant begins taking any of the drugs while on-study, he/she will not be discontinued.

APPENDIX III

Capsule Dosing Tables

WT_Low	WT_High		mg/kg/day_low	mg/kg/day_high	Goal	Total Daily Dose
20	20	150/150/150/150	30.0	30.0	30 mg/kg/day	600
21	30	300/300/300	30.0	42.9	30 mg/kg/day	900
31	40	300/300/300/300	30.0	38.7	30 mg/kg/day	1200
41	45	450/450/450	30.0	32.9	30 mg/kg/day	1350
46	60	450/450/450/450	30.0	39.1	30 mg/kg/day	1800
61	72	750/750/750	31.3	36.9	30 mg/kg/day	2250
73	80 >81	600/600/600/600 900/900/900	30.0	32.9	30 mg/kg/day	2400 2700
20	25	300/300/300	36.0	45.0	40 mg/kg/day	900
26	32	300/300/300/300	37.5	46.2	40 mg/kg/day	1200
33	38	450/450/450	35.5	40.9	40 mg/kg/day	1350
39	48	450/450/450/450	37.5	46.2	40 mg/kg/day	1800
49	56	750/750/750	40.2	45.9	40 mg/kg/day	2250
57	64 >64	600/600/600/600 900/900/900	37.5	42.1	40 mg/kg/day	2400 2700

APPENDIX IV

Clindamycin in Non-Obese Children

Ref	*PO clindamycin:*			*Dose 1*		*Dose 13*	*Dose 17*		
	Dose Amount	Age range (years)	*No. Subjects*	C_{max} (1 hour) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{max} (1 hour) (mcg/mL)	Half-life (h)	AUC (mcg/mL * h)
14	2 mg/kg	7-12	11	1.24 (0.70)	0.19 (0.27)	0.72 (0.21)	2.46 (0.68)	1.51 (0.74)	4.64 (2.11)
14	3 mg/kg	6-12	11	2.25 (0.53)	0.44 (0.19)	1.23 (0.31)	2.98 (0.93)	1.98 (0.60)	9.28 (2.71)
14	4 mg/kg	8-14	10	2.44 (0.65)	0.51 (0.25)	1.45 (0.36)	3.79 (0.61)	2.22 (0.78)	9.35 (3.23)
14	2 mg/kg	3-7	13	1.22 (0.51)	0.18 (0.23)	0.55 (0.17)	2.21 (0.51)	-	-
14	2 mg/kg	0.5-2	8	1.22 (1.14)	0.30 (0.37)	0.60 (0.32)	2.53 (0.86)	-	-
	IV clindamycin:			*Dose 1*					
				C_{max}	Half-life (h)				
5	5-7mg/kg	Pediatric patients”		10	2.5				

*All values are means (standard deviation).
C_{max} – maximum concentration; C_{min} – minimum concentration; AUC – area under the concentration time curve.

Pediatric Trials Network

Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLN01

Phase I Trial

Funding Sponsor:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Funding Mechanism: Task Order

Protocol Number:	NICHD-2012-CLN01
Protocol Date:	08-May-2014
Protocol Version:	6.0
IND Number:	115,396 (P. Brian Smith, IND holder)
Principal Investigator:	Michael J. Smith, MD, MSCE Associate Professor of Pediatrics University of Louisville Louisville, KY 40202 Telephone: Redacted Fax: Redacted E-mail: Redacted

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to, 45 CFR 46 (Human Subjects Protection, incorporating Subpart D: Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D: Additional Safeguards for Children in Clinical Investigations), and 21 CFR 56 (Institutional Review Board [IRB]).

All individuals responsible for the design and/or conduct of this study have completed human subjects protection training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTIGATOR STATEMENT

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

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

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

_____
Principal Investigator Name (Print)

_____ _____
Principal Investigator Signature Date

STUDY PRINCIPAL INVESTIGATOR / IND SPONSOR SIGNATURE

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

Principal Investigator
Pediatric Trials Network Study

Principal Investigator Signature

Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Concentration Time Curve
BPCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cl	Clearance
Cl/F	Oral Apparent Clearance
CRF	Case Report Form
CYP	Cytochrome
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
ECLS	Extracorporeal Life Support
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mg	Milligram
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*

LIST OF ABBREVIATIONS (continued)

N	Number (typically refers to participants)
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NPO	Nothing by Mouth
PD	Pharmacodynamics
PG	Pharmacogenomic
PK	Pharmacokinetics
PO	Oral
PTN	Pediatric Trials Network
SAE	Serious Adverse Event
$T_{1/2}$	Half-life
TBW	Total Body Weight
Vd	Volume of Distribution
V/F	Oral Apparent Volume of Distribution

PROTOCOL SYNOPSIS

Protocol Title:	Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin in Pediatric Subjects with BMI ≥ 85th Percentile (NICHD): CLN01
Phase:	I
Product:	Clindamycin phosphate (intravenous) Clindamycin hydrochloride (oral capsules) Clindamycin palmitate (oral solution)
Objectives:	Primary: Determine the pharmacokinetics (PK) of intravenous clindamycin in overweight and obese children and adolescents Secondary: 1) Determine the PK of oral clindamycin in overweight and obese children and adolescents 2) Characterize the safety profile of clindamycin in overweight and obese children and adolescents
Study Design:	Prospective, multi-center, open-label, multiple-dose PK study of intravenous and oral clindamycin
Study Population:	Children ages 2 – <18 years of age with body mass index (BMI) ≥85 percentile for age
Number of Participants:	24–32 evaluable participants
Number of Sites:	Up to 8 sites
Duration of Subject Participation:	Up to 18 days (1-day screening period, maximum of 14-day treatment period, and 3-day observation period)
Dose Schedule:	30–40 mg/kg/day dosed every 6 or every 8 hours with a maximum daily dose of 2.7 grams/day. Dosing greater than 2.7 g/day will be allowed for children receiving clindamycin as standard of care.
Estimated Start:	October 2012
Estimated Time to Complete Enrollment:	Approximately 24 months

PROTOCOL SYNOPSIS (continued)

Inclusion Criteria:	1) 2 years – <18 years of age at the time of first dose of study drug 2) Suspected or confirmed infection OR receiving intravenous clindamycin per routine care 3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours prior to the first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug 4) BMI ≥85th percentile for age and sex, based on CDC recommendations 5) Obtained informed consent/HIPAA from the parent/legal guardian and assent (if applicable)
Exclusion Criteria:	1) The following apply only to those who are NOT already receiving clindamycin per routine care: a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin b. History of *C. difficile* colitis with previous administration of clindamycin c. AST >120 units/L d. ALT >210 units/L e. Total bilirubin >3 mg/dL f. Serum creatinine >2 mg/dL g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II.B**) 2) Previous participation in the study 3) Current exposure to medication listed in **Appendix II.A** 4) Participant is receiving extracorporeal life support (ECLS) 5) Participant is post-cardiac bypass (within 24 hours) 6) Participant on inotropes/pressors 7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

Table 1. Study Event Table

Study Event/Day	Baseline/ Day 0	Study Days 1-14	End of Therapy (Day 14) OR Early Withdrawal or Discontinuation	3-Day Post-Treatment Phone Follow-up
Informed consent/ assent & HIPAA	X			
Medical history	X			
Demographics	X			
Concomitant medications of interest	X	X	X	X
Culture results (if available)	X	X		
Physical examination	X		X	
Weight	X			
Height	X			
BMI	X			
Waist:hip ratio	X			
Laboratory evaluation[a]	X		X	
α-1 glycoprotein (will be done by OpAns at their lab)[b]	X			
Laboratory evaluation (**6.6.1 Table 2**—if obtained as part of routine care)		X		X
Serum pregnancy test (female only)	X			
Feeding status (during PO PK portion only)		X		
Discarded scavenged plasma[c]		X	X	
Clindamycin IV or PO[d]	X	X[f]		
PK samples[e]		X		
AE/SAE	X	X	X	X

[a] Hemoglobin, hematocrit, platelets, white blood cells, sodium, potassium, chloride, bicarbonate, total calcium, glucose, creatinine, blood urea nitrogen, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin.

[b] Central laboratory will measure this from plasma sample collected per PK schedule.

[c] Discarded plasma may be collected after the first dose of study drug through 24 hours after the last dose of study drug.

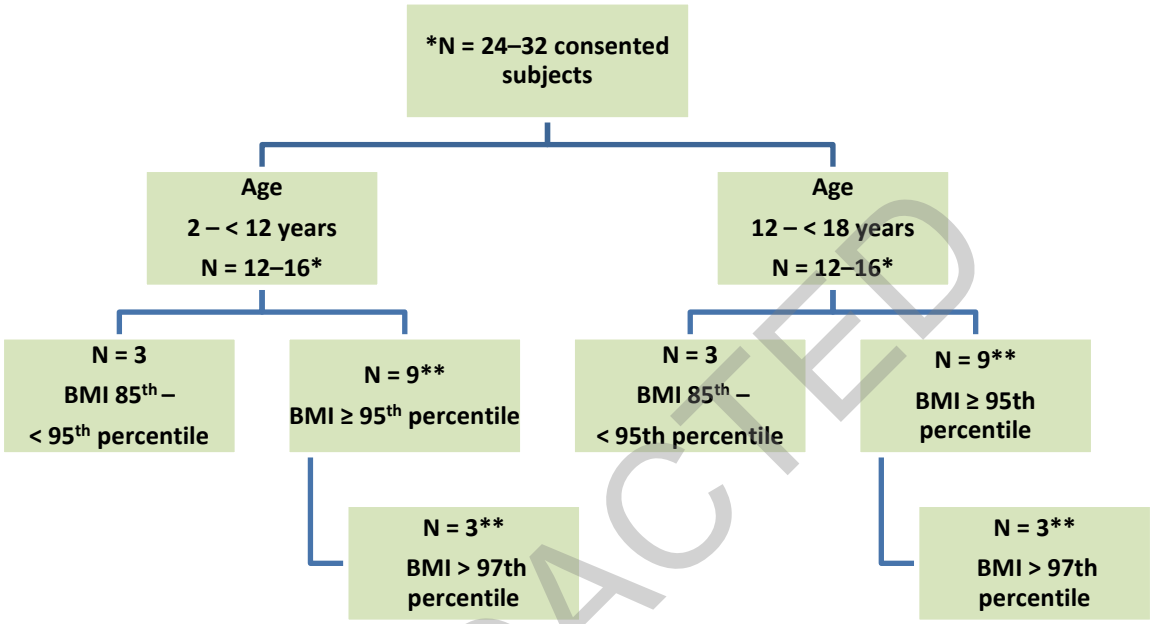
[d] Group assignment (see **Figure 1**).

[e] PK sampling (**Table 3**, see **Section 6.6.2**).

[f] IV clindamycin will be continued per treating physician; when switched to PO, participant will also participate in PO PK study.

Note: Day 0 and Day 1 can be same date, i.e., if consent obtained on same date as first study dose administration.

Figure 1. Schematic/Description of Study Design



* IV participants who transition to oral clindamycin will also participate in the oral PK study.

** Minimum of 3 participants with BMI > 97th percentile in each age group.

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Over the past decade, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a leading cause of hospitalization for children and adolescents in the United States (1). Consequently, the use of antimicrobial agents active against MRSA has become more prevalent (2). Specifically, the use of clindamycin among children hospitalized with *Staphylococcus aureus* infections increased from 21% in 1999 to 63% in 2008. At the same time, rates of childhood obesity have continued to remain high. Recent national data demonstrate that 17% of children aged 2–19 years in the United States are obese (body mass index [BMI] ≥ 95th percentile) and 12.3% are morbidly obese (BMI ≥ 97th percentile) (3). Obese patients have a greater likelihood of complications from infectious diseases and are at increased risk of developing *Staphylococcus aureus* infections. Therefore, an understanding of the PK of clindamycin in this population is critical to ensure appropriate interventional therapy.

Clindamycin, a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin (4), is approved by the U.S. Food and Drug Administration (FDA) for the treatment of pediatric and adult patients with respiratory tract, female pelvis and genital tract, and skin and soft tissue infections with susceptible bacteria including streptococci, pneumococci, and staphylococci. Clindamycin is also approved in adults for septicemia and intra-abdominal and serious infections with susceptible anaerobic bacteria (5).

Clindamycin is approximately 90% protein-bound. It is metabolized by the liver and excreted via the liver, bile, and kidneys. Impaired renal function modestly decreases the elimination of clindamycin; however, dosage adjustment is not required with renal dysfunction (4). Clindamycin phosphate (intravenous [IV] formulation) is rapidly converted to active clindamycin which has an elimination half-life of about 3 hours in adults and 2.5 hours in children (5). The drug penetrates well into all tissues, with the exception of the brain and cerebral spinal fluid. It is actively taken up and concentrated within the phagocytic cells. Clindamycin binds to the 50S subunit on the bacterial ribosome and inhibits protein synthesis by interfering with the formation of initiation complexes, thus inhibiting exotoxin production (4). Clindamycin exhibits time-dependent killing; and efficacy is correlated with the time clindamycin concentrations exceed the minimum inhibitory concentration of the pathogen of interest. A summary of clindamycin serum concentrations in non-obese children is found in **Appendix IV**.

Variability in serum and tissue concentrations has been reported in obese patients (4). The underlying premise is that this is due to physiologic changes that alter a drug's volume of distribution (Vd) and body clearance (Cl) (6,7). Thus, obese patients may be dosed inappropriately if fixed or "adult" doses are used (under-dosed) or if weight-based dosing is used (over-dosed) (6,7). Because critically ill obese patients with infections are reported to have a worse outcome than non-obese patients (8), it is imperative to determine if the disposition of and response to clindamycin may be altered compared to healthy children with an infection. In addition, sub-therapeutic drug concentrations may increase the development of resistant

organisms. Thus, it is important to perform pharmacokinetic (PK) and pharmacodynamic (PD) studies in the obese pediatric population to ensure that these patients are being optimally dosed with medications designed to treat infections. There are no currently available PK (or PD) data to guide clindamycin dosing in obese pediatric or adult patients. This proposal will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years.

2.2 Scientific Rationale

Selection of the correct drug dose and dose regimen is the most important decision in ensuring optimal pharmacotherapy. Defining an optimal regimen requires a clear understanding of the drug's PK, PD, and, for many compounds, pharmacogenomic (PG) profiles. Understanding these characteristics for drugs used in pediatrics is imperative to determine optimal dose regimens across the pediatric age continuum.

Clinically, drug dosing in pediatrics is individualized to age by basing the drug dose on a patient's body weight and the dose interval on the functional capacity of the drug's clearance pathways. This approach assumes, though inaccurately, that a drug's Vd and body Cl are directly proportional to a patient's body weight. Despite this lack of proportionality, the majority of pediatric patients favorably respond to weight-based drug dosing. However, as the potency of newer drugs increases and the need for more precise drug dose regimens expands, better-defined dose regimens based on careful assessment of the drugs' integrated PK-PD-PG profiles across the pediatric age continuum are needed (9). Complicating this paradigm are the substantially increasing numbers of children and adolescents who are obese, and even morbidly obese, and the lack of data on disposition in the obese population. Clinical trials of new drugs focused on FDA labeling exclude obese patients, leaving the determination of dosing regimens in the obese for post-marketing, often investigator-initiated studies.

Antibiotic Dosing Regimens Based on PK-PD Modeling
Prior to our understanding of the integrated PK-PD characteristics for antibiotic drugs, antibiotic dosing regimens were mostly based on perceived maximum tolerated doses often related in some manner to the target pathogen minimum inhibitory concentration (MIC). Integration of an antibiotic's PK with PD allows for the determination of the optimal dose regimen across the spectrum of antibiotic drugs (10,11). In addition, this more quantitative approach permits comparisons of different antibiotic drugs for a specific infection and far more accurate predictability of patient response. The specific antibiotic PK-PD characteristic used to predict outcome (i.e., bacteriologic eradication) appears to be mostly dependent on whether the drug's bacterial killing is concentration- or time-dependent. Clindamycin is most often described as a "time-dependent antibiotic with moderate persistent effects," and as such, the best predictor of bacterial killing appears to be the ratio of the area under the clindamycin (free, unbound) drug concentration time curve (AUC) divided by the targeted pathogen MIC (i.e., fAUC/MIC) (11). To accurately determine this pivotal PK-PD parameter, what is needed is a comprehensive understanding of the drug's PK profile across the age spectrum while incorporating the spectrum of pathophysiologic changes and differing body habitus. For clindamycin, these data are not available.

Clindamycin Pharmacokinetics
Limited published clindamycin PK data exist and encompass < 100 neonates, infants, and children. In neonates, clindamycin elimination is delayed compared with older infants and

children—mean elimination half-life (t ½) values of 8.7 vs. 3.6 hours, respectively (12,13). Regardless of age group studied, variability was observed in clindamycin t ½, Vd, AND systemic Cl. In addition, some studies report variable serum clindamycin concentrations (bioactivity) following parenteral dosing (12,14). Despite this variation in drug disposition, which is observed in both children and adults, bioactive serum clindamycin concentrations remain therapeutic following routine parenteral (intramuscular, IV) or oral dosing. Considering that clindamycin, an antibiotic, is used to treat infections caused by susceptible pathogens responsible for infectious diseases regardless of patient age, pediatric clindamycin development strategies need only focus on the drug's safety and PK profile to ensure similar systemic exposure. Available clindamycin PK data support close similarity for clindamycin systemic exposure (i.e., bioactive serum clindamycin concentrations and AUC) in older infants, children, and adults following comparable mg/kg doses (12, 14–19). As noted above, clindamycin PK in premature and full-term infants is, as expected, different than that observed in older patients (12,13). This foundation of data underscores the importance of studying clindamycin disposition in the obese pediatric patient.

Clindamycin is extensively bound to plasma protein, primarily to alpha 1 acid glycoprotein, and, with the exception of the brain or cerebrospinal fluid, effectively penetrates body tissues and fluids. The drug is metabolized primarily by the cytochrome (CYP) P450 isoenzyme CYP3A4 to two primary, antimicrobial active metabolites, a sulfoxide and to a lesser extent N-demethylclindamycin (20). Although only limited data are available for current clindamycin pediatric dosing regimens, the regimens employed clinically have been used for decades with apparent success. Nevertheless, clindamycin optimal dosing regimens in pediatrics remain unknown. Furthermore, the influence of obesity on clindamycin disposition is unknown and may have a far greater negative impact on patient outcome due to ill-defined, clinically extrapolated dosing.

Drug Dosing and Obesity

Data defining optimal drug dosing in the obese and morbidly obese adult patient are very limited and virtually non-existent in pediatrics. Drug dosing on total body weight (TBW) in the obese patient has the real risk of overdosing the patient, resulting in an increased incidence of adverse effects, while dosing on ideal body weight (IBW) can lead to serious under-dosing. In obese adults, IBW is increased by 20–40%, which is unaccounted for when using the many mathematical formulas available to calculate dosing based on a person's IBW. This deficiency may partially explain the inaccuracy of drug dose regimens for obese patients based on IBW formula estimations (21–26).

The influence varying degrees of obesity have on important physiologic functions across the age continuum in pediatrics is unknown. In adults, sparse data suggest that obese adults may have altered tissue blood flow rates due to inherent differences in blood flow to lean (greatest amount) and adipose tissue, impaired cardiac function, and alterations in phase I and II metabolism. Although intuitive, one might assume that a drug's Vd would be increased in obese patients for lipophilic compounds, though in fact, for the few drugs assessed, the Vd is highly variable. Similarly, Cl is also highly variable in the obese population, underscoring the need to determine drug disposition characteristics not only across the age continuum but also with increasing degrees of obesity (21–24). No such data are available for the pediatric patient, but these data combined underscore the need to critically assess a drug's disposition relative to age and body habitus. Furthermore, for antibiotics whose efficacy is dependent on achieving

effective concentrations at the infectious site, interfaced with the organism, optimal dosing in the obese pediatric patient must be defined (6,7).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of Blood Draws
There are small risks to blood sampling, usually some pain/discomfort with the blood stick. Every effort will be made to avoid additional (to standard of care) sticks for this study by timing clinical blood draws to coincide with timed samples when possible and the use of existing IV lines when feasible for the blood draws.

Risks of Clindamycin
From the FDA label and review of the literature, the following are adverse reactions of clindamycin: antibiotic-associated colitis, pseudomembranous colitis, abdominal pain, nausea, and vomiting; hypersensitivity reactions (maculopapular rash and urticaria have been observed during drug therapy; generalized mild-to-moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions; rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin; a few cases of anaphylactoid reactions have been reported). Organ systems that are affected include skin and mucous membranes (pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported); liver (jaundice and abnormalities in liver function tests have been observed during clindamycin therapy); renal system (although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances); hematopoietic (transient neutropenia [leukopenia] and eosinophilia have been reported; reports of agranulocytosis and thrombocytopenia have been made; no direct etiologic relationship to concurrent clindamycin therapy could be made in any of these instances); local reactions (pain, induration, and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion); musculoskeletal (rare instances of polyarthritis have been reported); cardiovascular (rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV administration). There is minimal additional risk to the participants who are receiving clindamycin as part of their routine medical care.

2.3.2 Known Potential Benefits

The participant may benefit from the use of the study drug; however, participation in this study has no other potential benefits to the participants. The results of this study may benefit overweight and obese participants in the future who require clindamycin therapy.

3 OBJECTIVES

Primary Aim
Characterize the PK of multiple-dose IV clindamycin in overweight and obese children and adolescents.

Secondary Aims
1. Characterize the PK of multiple-dose oral clindamycin in overweight and obese children and adolescents.
2. Characterize the safety profile of clindamycin in overweight and obese children and adolescents.

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1. PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUC_{tau})

3.1.2 Secondary Outcome Measures

1. PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2. Safety profile: Adverse events will be collected during and after study drug administration.

4 STUDY DESIGN

This will be a prospective, open-label PK and safety profile study of multiple doses of IV and oral clindamycin in overweight and obese children 2 – < 18 years of age. The total study duration is expected to be approximately 24 months; each participant will participate in the study for up to 18 days (screening day; treatment days 1–14 followed by an observation period of 3 days post discontinuation of clindamycin therapy or after day 17 [on day 18] of therapy in those who are treated with more than 14 days of clindamycin).

5 Study Population

Selection of the Study Population
Eligible participants ages 2 – <18 years will be identified through the inpatient units at each participating site. There will be up to 32 evaluable participants (defined in **Section 10.3**) enrolled; however, target enrollment will be 24 participants. If dosing changes are suggested by the interim PK analysis (see **Section 10.3**), approximately 8 additional participants will be enrolled. Twelve to 16 participants will be enrolled in each of the following age groups: 2– <12 years and 12 – < 18 years of age. Participants will be further stratified into 1 of 2 groups based on their BMI (85th – <95th percentile, and ≥95th percentile). No more than 3 participants with BMI in the 85th – <95th percentile will be enrolled in each age group. Participating sites will prioritize enrollment of participants with BMI >97th percentile in each age group.

5.1 Inclusion/Exclusion Criteria

The investigator or other study site personnel will document in the source documents (e.g., the hospital chart) that informed consent and assent (if applicable) were obtained. Laboratory tests or non-pharmacologic treatment procedures that were performed and considered "routine care" within 72 hours of first dose of study drug may be used for screening procedures required by the protocol and recorded in the case report form (CRF).

Inclusion Criteria

1) 2 years – < 18 years of age at the time of first dose of study drug
2) Suspected or confirmed infection OR receiving IV clindamycin per routine care
3) Negative serum pregnancy test (if female and has reached menarche) within 24 hours prior to first dose of study drug and agreement to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy test through the last dose of study drug
4) BMI ≥ 85th percentile for age and sex, based on CDC recommendations
5) Obtained informed consent/HIPAA from the parent/legal guardian and assent (if applicable)

Exclusion Criteria

1) The following apply only to those who are NOT already receiving clindamycin per routine care:
   a. History of hypersensitivity or allergic reaction to clindamycin or lincomycin
   b. History of *C. difficile* colitis with previous administration of clindamycin
   c. AST > 120 units/L
   d. ALT > 210 units/L
   e. Total bilirubin > 3 mg/dL
   f. Serum creatinine > 2 mg/dL
   g. Receiving a neuromuscular blocker as part of their therapy (see **Appendix II.B**)
2) Previous participation in the study
3) Current exposure to medication listed in **Appendix II.A**

4) Participant is receiving extracorporeal life support (ECLS)
5) Participant is post-cardiac bypass (within 24 hours)
6) Participant on inotropes/pressors
7) Any other condition or chronic illness that, in the opinion of the principal investigator, makes participation unadvised or unsafe

5.2 Treatment Assignment Procedures

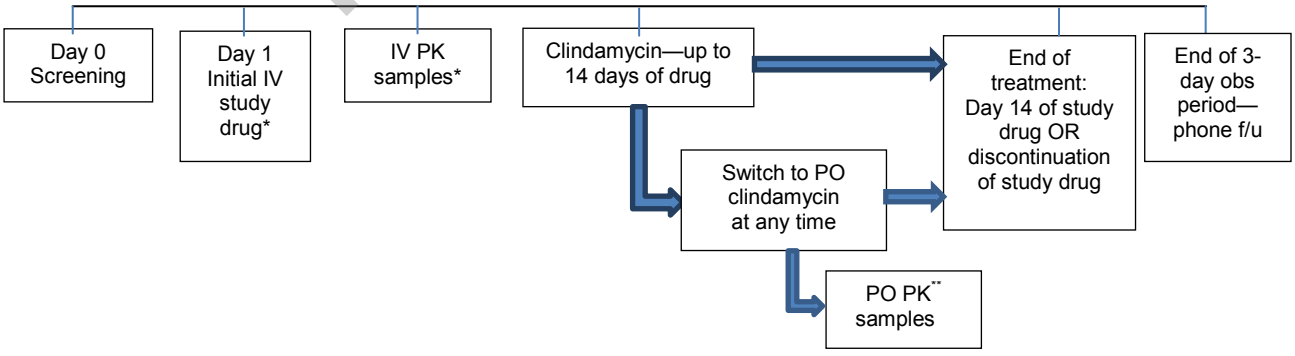
This will be an open-label PK study. Participants will be assigned to age groups based on age upon first dose of study drug and to a BMI group based on BMI obtained at baseline (Day 0). The study drug is defined as dose(s) given after consent.

5.2.1 Duration of Study Participation

Duration of therapy will be up to 14 days for children who receive the first dose of IV clindamycin as the study drug. The total duration of therapy with clindamycin will be determined by the treating physician for those children who are receiving clindamycin as part of routine care; however, only 14 days of therapy will be considered as study drug. Study follow-up will occur 3 days (+/- 1 day) after the last dose of study drug. Patients who are receiving antimicrobial agents other than clindamycin may enroll in this study and receive up to 3 doses of IV clindamycin and 4 doses of oral clindamycin in addition to their standard of care therapy. Participants who transition to oral clindamycin may return as outpatients to complete the PK portion of the study.

Total duration of study participation will be up to 18 days. This will comprise a 1-day screening period; a maximum 14-day treatment period; and a 3-day post-study observation period to monitor for serious adverse events. The 3-day post-treatment visit may be a phone follow-up. Patients may continue clindamycin per their physician's recommendation after they have completed participation in this (maximum of) 18-day study.

Figure 2.Timeline



* Minimum of 1 dose of IV clindamycin before IV PK period (see **Section 6.6.2** for further details).

** Minimum of 3 doses of PO clindamycin before PO PK period.

5.2.2 Replacement Participants

Participants in the IV portion of this study who are unable to provide at least 3 timed PK samples may be replaced.

5.2.3 Reasons for Participant Withdrawal

A participant or his/her parent/guardian may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the participant from participating in this study at any time. Participants may be prematurely discontinued from the study for any of the following reasons:

- Participant or investigator noncompliance with the study protocol
- At the request of the participant, investigator, treating physician, or sponsor
- Adverse reaction or suspected adverse reaction.

Participants are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. The participant who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations, and will be provided appropriate care under medical supervision until the symptoms of any adverse event (AE) resolve or the participant's condition becomes stable. Participants withdrawn from the study due to an AE must be followed per protocol (see **Section 8.2.4**).

5.2.4 Termination of Study

This study may be terminated at any time by NICHD, the Investigational New Drug Application (IND) sponsor, or the Data Monitoring Committee (DMC) if serious adverse reactions occur in 2 or more participants that are directly related to study drug, or if, in NICHD's judgment, there are no further benefits to be achieved from the study. A study site may be terminated if the investigator does not adhere to the study protocol.

6 STUDY PROCEDURES

6.1 Summary of Procedures

See the schedule of study events and procedures (**Table 1**).

1. Medical history will be obtained by interview with the parent/legal guardian/participant and from the participant's medical records.
2. Concomitant medications of interest administered within 7 days prior to first study dose and during the period of administration of study drug, including herbal products of interest, will be recorded (see **Appendix II**).
3. Physical examination, including abnormal physical findings, height (measured standing if possible), weight and waist:hip ratio will be obtained (see **Section 6.3 #2**).
4. Safety laboratory testing (see **Section 6.6.1)**
5. PK sampling (see **Section 6.6.2**).

6.2 Screening

Research staff at sites will screen potential participants for eligibility requirements per local institutional policies.

6.3 Enrollment/Baseline

Baseline Assessment (Day 0)
After the parent or legal guardian has provided informed consent /HIPAA, the participant has provided assent (if applicable), and after it has been determined that the participant satisfies all inclusion and no exclusion criteria, the following evaluations will be performed and recorded in the CRF:

1. Participant demographics
2. Physical exam.
   NOTE: The initial physical examination information (except the height, weight, and waist/hip measurements) may be obtained from the medical record but must have been performed within 24 hours prior to first study dose. Height, weight and waist/hip measurements must be performed after consent. BMI will be calculated from height and weight using the following formula: BMI = [weight (kg) / (stature (cm))^2] x 10,000. Refer to the Centers for Disease Control (CDC) pediatric BMI calculator (http://apps.nccd.cdc.gov/dnpabmi/) to determine the BMI percentile. The BMI percentile will be obtained using the BMI calculator and verified using the age- and sex-specific CDC BMI charts (see **Appendix I**).
3. Pertinent medical history
4. Concomitant medications of interest (7 days prior to first dose of study drug) (see **Appendix II**)

5. Laboratory determinations (see **Table 2**, **Section 6.6.1**)
6. Culture results of blood, urine, sputum, or wound (if obtained as part of routine care) within 72 hours prior to the first dose of study drug
7. For participants receiving clindamycin per routine care, the date and time for the doses administered prior to first dose of study drug will be recorded (up to a maximum of 6 prior doses)
8. Serum pregnancy test (females only who have reached menarche) within 24 hours prior to first dose of study drug.

Assessments/Procedures (Days 1–14)
The participant will start study drug upon completion of the baseline procedures. Standard of care dosing may need to be increased to comply with the protocol; refer to **Section 7.1.2** for specific dosing information. Participants who transition to oral therapy will also participate in the oral-dose PK portion.

The following assessments will begin with the first dose of study drug and continue throughout therapy up to Day 14:

1. Concomitant medications of interest (see **Appendix II**)
2. Start date/time and stop date/time of clindamycin administration and flush date/stop time after IV administration
3. Feeding status (during PO PK portion only): nothing by mouth (NPO), clear liquids, full feeds, etc.
4. Collection of PK samples (including date/time) (see **Section 6.6.2**)
5. Results for laboratory tests of interest (see **Section 6.6.1**)
6. Collection of culture results (if available)
7. Adverse events (see **Section 8.2.1**)

6.4 End of Therapy OR Early Withdrawal/Discontinuation

The following assessments will be conducted at early withdrawal or end of therapy:

1. Concomitant medications of interest (see **Appendix II**)
2. Physical examination
3. Laboratory evaluations (see **Section 6.6.1**)
4. Adverse events (see **Section 8.2.1**)

6.5 Follow-up Safety Phone Call

Assessments/Procedures (Day 3 Post Treatment): This visit will be a phone follow-up unless the participant is still hospitalized, in which case an in-person visit or chart review may be performed. This assessment will occur 3 days (+/- 1 day) after the last dose of study drug (i.e., end of therapy or early withdrawal/discontinuation). The following information will be obtained:

1. Adverse events (see **Section 8.2.1**)
2. Concomitant medications of interest (**Appendix II**)
3. Results for laboratory tests of interest (see **Section 6.6.1**)

6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

Laboratory testing (**Table 2**) will be collected on all participants and be performed in the local laboratory at each site. Laboratory values will be collected within 72 hours prior to the first dose of study drug through 3 days (+/- 1 day) after the last dose of study drug. If multiple values for a laboratory are obtained in the 72 hours prior to start of first study dose, record the value closest to the start of first study dose. Laboratory values performed as part of routine care within 72 hours prior to the first dose of study drug may be used for baseline laboratory tests. Laboratory values will also be obtained at the end of therapy. Laboratory values obtained within ± 24 hours of discontinuation of study drug or within ± 24 hours of completion of 14 days of study drug (if participant is continuing clindamycin beyond 14 days) may be used as end-of-treatment laboratory values. If the baseline and end of therapy laboratory tests have not been performed as part of routine care, they will be performed for the study per the protocol schedule. The serum pregnancy test will also be performed at the local laboratory. Alpha (α)-1-glycoprotein will be measured from one of the PK samples by the central laboratory once during the study using an ELISA kit (central laboratory). Sites do not need to collect an extra sample to measure α-1-glycoprotein.

Table 2. Laboratory Evaluations

Hematology	Serum Biochemistry
Hemoglobin Hematocrit Platelets White blood cells	Sodium Potassium Chloride Bicarbonate Total calcium Glucose Creatinine Blood urea nitrogen Total protein Albumin Aspartate aminotransferase Alanine aminotransferase Bilirubin

6.6.2 Special Assays or Procedures

PK Samples
Blood (0.5 mL) will be collected with scheduled IV and oral doses of clindamycin for clindamycin plasma concentration determinations (see **Table 3** below for schedule). In participants receiving IV clindamycin, PK samples should be collected from a site separate from the site of administration.

PK samples (#1-6) will be obtained at any point after the first study dose. For PO clindamycin, PK samples will begin with any dose after the 3rd dose of PO study drug (first PK sample obtained within 15 minutes prior to PO study dose #4 or later).

However, if each of the following criteria are met, PK samples (1-6) can be obtained at any point after consent:

- The most recent pre-consent standard of care dose is the same dose/interval/route as post-consent on-study doses
- Exact start and stop times of the pre-consent dose are clearly documented (estimated times are not acceptable), AND
- Exact flush time of the pre-consent dose is clearly documented. Estimated flush times are not acceptable unless there is documentation of site standards for infusion/flush periods.

The PK samples will be drawn according to the following schedule relative to the end of flush (IV PK) or actual time of oral administration (PO PK).

Table 3. PK Schedule

	Scheduled PK Sampling Times				
	Time (Hours)*	**IV Dose***		**PO Dose**	
PK Sample		**Q6h**	**Q8h**	**Q6h**	**Q8h**
1	Pre-dose 0 (within 15 minutes prior to the dose)	**X****	**X****	**X****	**X****
2	0.5 (± 5 minutes)	**X****	**X****	N/A	N/A
3	1–1.5	X	X	**X****	X**
4	3–4	**X****	**X****	**X****	--
5	5–6	--	X	--	**X****
6	Pre-dose (will depend if on q6h or q8h dose schedule)	**X****	**X****	**X****	**X****
Total number of samples		5	6	4	4

* Time starts at end of flush after the 30-minute infusion.

** Priority samples (see paragraph below).

Every effort should be made to collect all PK samples for each participant. Collection of PK samples should be timed with collection of laboratory tests per standard of care to minimize blood draws specifically for the study. If it is impractical to collect all PK samples during the same dosing interval, samples can be obtained at different dosing intervals. If it is impossible to obtain all PK samples for each participant, **PK samples can be prioritized to include:**

a) **For IV administration: pre-dose, 0.5 hours, 3–4 hours, and pre-next dose**

b) **For oral administration: pre-dose, 1–1.5 hours, 3–4 hours (q6h dosing), 5–6 hours (q8h dosing), and pre-next dose**

Clindamycin concentrations in plasma will be measured at a central laboratory using a validated bioanalytical assay. In addition, scavenged samples will be obtained.

Scavenged Plasma Sampling
Plasma samples collected in EDTA tubes during the course of therapy (~100 µL plasma or ~200 µL whole blood) will be procured, after consent. A maximum of 10 scavenged plasma samples will be collected per participant. Collection may begin with any specimen collected after the first dose of study drug through 24 hours after the last dose of study drug. The date and time of sample collection, as well as the date and time the sample is frozen, will be collected for all scavenged samples.

Minimizing Blood Loss
To minimize the amount of blood sampling, laboratory values will be obtained only at baseline and end of study. If they have been obtained as part of routine care within 72 hours prior to first dose of study drug, the baseline laboratory values do not need to be repeated. The PK sampling scheme will be employed such that no more than a total of 8 mL (< 3 mL/kg) of blood is obtained from each participant for PK analysis. Plasma samples will be collected in 0.5 mL blood aliquots.

6.6.3 Specimen Preparation, Handling, Storage, and Shipping

Detailed information for collection, labeling, preparation, handling, storage, and shipping of specimens is detailed in the manual of procedures (MOP).

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

A dose of 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 g/day is selected based on current labeling. Patients who are receiving clindamycin as part of their routine care are also eligible to participate if their dose can be adjusted to be at least 30 mg/kg/day upon enrollment. The dose administered will be based on TBW. Because bioavailability is estimated at 85%, the same dose will be used for oral administration as is used for IV dosing. Both solution and capsule preparations will be included in this study because both oral formulations are used in clinical practice, and it will allow the inclusion of those patients who cannot swallow pills. In the absence of PK data, we assume that drug clearance will be comparable in obese pediatric patients compared to non-obese pediatric patients. Therefore, a dosing regimen 30–40 mg/kg per day and a maximum dose of 2.7 g/day should provide exposures similar to those used in children and adolescents with a normal BMI. It is predicted to be safe in the obese population because similar doses are currently used per routine care.

7.1.2 Dose and Timing

Both q6h and q8h dosing will be allowed for both oral and IV dosing of clindamycin. For children receiving clindamycin as part of clinical care, this protocol will not prescribe a route of administration or dosing interval; the dose, route of administration, and dosing interval prescribed by the treating physician will be recorded on the CRF. However, if the prescribed dose is less than the lowest dose for this study, the dose of clindamycin will be changed to comply with the study dose. Dosing greater than 2.7 g/day will be allowed for children receiving clindamycin as part of clinical care. See **Section 5.2.1** for duration of therapy.

IV dosing: A minimum of 2 study doses of IV clindamycin will be administered. The dose administered will be based on TBW at 30–40 mg/kg/day divided q6h or q8h with a maximum dose of 2.7 grams/day. The drug will be administered over 30 (+/– 5) minutes. The venous access line will be flushed per local practice after completion of IV administration, and the time of the end of flush will be documented. It is preferred that the flush be ≤1 minute after the end of infusion.

Oral dosing: For those participants who are receiving clindamycin as a solution, they will receive 30–40 mg/kg/day divided q6h or q8h. For those participants receiving the capsule formulation, they will receive the dose of clindamycin defined in **Appendix III**. Only whole capsules will be used. The oral solution will be used for those participants who cannot swallow capsules. No more than 12 PO study drug doses will be administered as part of this study.

7.1.3 Formulation, Packaging, and Labeling

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules.

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles for reconstitution.

Each formulation is approved for use in the United States.

7.1.4 Product Storage and Stability

Clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules), and clindamycin palmitate (PO oral solution) will all be stored at room temperature (20–25^0 C). Diluted clindamycin phosphate (IV) is stable at room temperature for at least 16 days and refrigerated for at least 32 days. Reconstituted clindamycin palmitate hydrochloride, USP for oral solution is stable for 2 weeks at room temperature and should not be refrigerated. See the MOP for detailed information.

7.2 Preparation and Administration of Study Intervention/Study Drug

Clindamycin phosphate, USP (IV) is supplied in vials with clindamycin 150 mg/mL and must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL. The drug will be infused over 30 (+/– 5) minutes. Infusion rates should not exceed 30 mg/minute. The pharmacy will prepare the IV formulation, and the dose administered will be based on TBW.

Clindamycin hydrochloride, USP (PO capsules) is available as 150 mg and 300 mg capsules, and the dose will be dispensed based on TBW (see **Appendix III** for dosing).

Clindamycin palmitate hydrochloride, USP for oral solution is available in 100 mL bottles and will be prepared in the pharmacy at each site based on the reconstitution recommendation in the label. The dose administered will be based on TBW.

Refer to the MOP for additional details regarding drug procurement, drug preparation, and administration.

7.3 Modification of Study Intervention/Investigational Product for a Participant

No dosing adjustments are required for hepatic or renal impairment.

7.4 Accountability Procedures for the Study Intervention/Study Drugs

Each site will provide drug for their study participants. The drug accountability records will be maintained according to sites' pharmacy policies and procedures for clindamycin phosphate (IV), clindamycin hydrochloride (PO capsules) and clindamycin palmitate (PO oral solution). See MOP for specific details related to investigational product accountability.

7.5 Assessment of Participant Compliance with Study Intervention

Compliance with dosing will be determined using the participant's medication administration record and other applicable site supporting documentation. For those participants who are discharged on oral clindamycin and have not completed the PO PK visit, the participant or parent/guardian will keep a drug administration diary and all drugs will be accounted for at the outpatient PK study visit. Outpatient study visits should be scheduled around the participant's oral dosing schedule to ensure that pre-dose samples are drawn at the study visit.

7.6 Concomitant Medications of Interest/Treatments

Concomitant medications of interest are listed in **Appendix II**. Children who are prescribed one of these medications after receipt of study drug may continue in the study.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

AEs will be collected during and after study drug administration and for 3 days following end of therapy with clindamycin. Results will be tabulated by MedDRA System Organ Class and Preferred Term.

8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

AEs will be collected from the time of consent, throughout the period of study drug administration, and for 3 days following end of therapy with clindamycin. See **Section 8.6** for clarification for AEs identified at the 3-day follow-up visit and for serious AEs (SAEs). Safety will be assessed by frequency and incidence of AEs and SAEs. The Best Pharmaceuticals for Children Act (BPCA) safety monitoring committee (DMC) convened by NICHD will review data and safety information from study participants.

8.2.1 Adverse Event

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

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

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

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

1. Death
2. Life-threatening AE (“life-threatening” means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

8.2.2 Unexpected Adverse Event

This is defined as any adverse event, the specificity or severity of which is not consistent with the package insert, investigational plan, or informed consent.

8.2.3 Identification of Events and Timeframe for Reporting

As all participants in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after consent has been obtained. The investigator will provide the date of onset and resolution, intensity, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome. Any event beginning more than 3 days after the last dose of study drug will not be captured.

8.2.4 Follow-up of Adverse Events

AEs ongoing at the time of the last dose of study drug will be followed up to 3 days after the last dose of study drug. AEs that resolve during the study or follow-up period will have the resolution date documented in the CRF. Adverse events that are identified at the last assessment visit/phone contact (or at the early termination visit) must be recorded on the AE CRF, with the status of the AE noted. Any events that are identified at the last assessment visit/phone contact will be followed for an additional 3 days for AEs and 10 days for SAEs and if still ongoing can be “resolved by convention”. All serious suspected adverse reactions will be followed until resolution. All enrolled participants in both cohorts who receive at least 1 dose of clindamycin will be followed for safety.

8.3 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. **MILD:** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. **MODERATE**: Participant experiences enough symptoms or findings to require intervention
3. **SEVERE**: Participant experiences symptoms or findings that require significant intervention

8.4 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction. ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

8.5 Reporting Procedures and Timeframe for Reporting

All AEs will be entered into the data system within 72 business hours of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties encountered when entering the event into the electronic data capture (EDC) system, the SAE will be reported to the data coordinating center (DCC) by telephone or FAX communication. Investigators must submit safety reports as required by their local IRB, independent of the reporting requirements specified in the protocol.

8.5.1 Serious Adverse Events

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC, IND sponsor, protocol chair, and funding sponsor (NICHD). The BPCA DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.5.2 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor. The sponsor or his representative will submit expedited safety reports (IND safety reports) to the FDA and other regulatory agencies as necessary, and will inform the DMC and investigators of such regulatory reports. Site investigators must submit IND safety reports as required by their IRB. Documentation of the submission to and receipt by the IRB should be retained for each IND safety report. The sponsor will submit a progress report of the investigation annually, which will include a summary showing the most frequent and most serious adverse events by body system.

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

Adverse events will be followed by the investigator or a clinician member of the study team in person if the participant is hospitalized for an AE or SAE. If the participant is not hospitalized, the investigator or a clinician may review the participant’s medical record, contact the participant by phone, or contact the participant’s primary care physician for follow-up.
Participants withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator. Refer to **Section 8.2.4** for follow-up of AEs/SAEs. The medical monitor or study principal investigator must be notified if the AE may relate to overdose of study treatment.

8.7 Halting Rules

Participant safety data will be reviewed on an ongoing basis to monitor for halting criteria.

The study enrollment and dosing will be halted for a safety review by the BPCA DMC if serious adverse reactions occur in ≥ 2 participants.

Furthermore, the NICHD, the IND sponsor, protocol chair, the DMC, and the investigators shall have the right to recommend termination of this study at their discretion. Possible reasons for termination of the study include, but are not limited to:

1. Adverse events
2. Unsatisfactory enrollment with respect to quantity or quality

The study may be placed on hold or terminated at a site(s) for the following reasons:

1. Inaccurate or incomplete data collection
2. Falsification of records
3. Failure to adhere to the protocol

8.8 Safety Oversight

This study will be overseen by the BPCA DMC, the NICHD, and the FDA. The DMC will review data from individual study participants on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study participants. This evaluation will also assess data quality and timeliness, participant recruitment, accrual, and retention. These reviews will allow the DMC to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DMC to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided.

Ad Hoc Meetings of the DMC: The DMC may convene an ad hoc meeting to discuss any issue of safety raised by an investigator, the IND sponsor, or a member of the DMC. At the discretion of the investigators, the sponsor, and DMC members, a non-serious AE that is 1) associated with the product and 2) does not meet the stopping rules criteria may be considered as a trigger for an ad hoc DMC meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCC or Duke Clinical Research Institute (DCRI) sponsor standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations, the DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan. Site visits will be made at standard intervals as defined by the clinical monitoring plans and may be made more frequently as directed by the IND and funding sponsors. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Study Outcome Measures

10.1.1 Primary Outcome Measures

1) PK parameters after multiple IV doses of clindamycin:
   - Clearance (Cl)
   - Volume of distribution (Vd)
   - Area under the curve (AUC_{tau})

10.1.2 Secondary Outcome Measures

1) PK results of patients transitioned to oral clindamycin:
   - Oral apparent clearance (Cl/F)
   - Oral apparent volume of distribution (V/F)

2) Safety: Adverse events will be collected during and after study drug administration.

10.2 Sample Size Considerations

It is anticipated that 12 children will be enrolled and treated in each of the IV groups for each age strata, leading to a total sample size of 24 participants. A sample size of 24 participants will provide adequate precision in the Cl/F PK parameter estimate. Assuming an inter-individual 40% coefficient of variation in the population Cl parameter estimate after weight-based allometric scaling, a sample size of 24 participants would provide a margin of error of ± 16% in the 95% confidence interval of the Cl estimate.

10.3 Analysis Plan

Population for Analysis
All participants that receive at least 1 dose of study drug will be included in the safety analysis. All participants with at least 1 evaluable PK sample will be included in the PK analysis plan. If participants have < 3 timed PK samples, additional participants may be enrolled to ensure appropriate analysis.

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

Demographics and Baseline Characteristics
The number of participants completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be summarized. Variables include race, ethnicity, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized by age and BMI cohorts.

Laboratory data, such as hematology and serum chemistry data, will be tabulated by age and BMI cohorts. Continuous laboratory measurements will be described using univariate 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.

Interim PK Analyses
An interim PK analysis of each age cohort will be performed after approximately 4 participants have been enrolled into that cohort. If an interim analysis suggests that PK data is required on more than 12 participants in that age cohort to evaluate the PK of clindamycin in this population, approximately 4 additional participants will be enrolled into that age group for a total of 16 participants.

PK Analysis
Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance. The influence of covariates (i.e., TBW, BMI, lean body weight, adjusted body weight, IBW, etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each participant. The plasma concentrations-time profiles of clindamycin will be presented in figure form by participant and cohort (age and weight/BMI). Descriptive statistics will be presented for continuous and categorical variables. A detailed description of PK/PD analyses can be found in the PK analysis plan. We will compare PK parameters in this study of obese children to non-obese children.

11 PARTICIPANT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. “Authorization” is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the participants' families. Consent forms describing in detail the study procedures and risks are given to the participant's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the participant's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant's legal guardian and answer any questions that may arise. The participant's legal guardian will provide informed consent prior to the participant being enrolled in the study. The participant's legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participant's legal guardian for their records. The rights and welfare of the participant will be protected by emphasizing to their legal guardian that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the participant's risk to receive the investigational product. This new information will be communicated by the investigator to participant's legal guardian who consented to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participant's legal guardian will be re-consented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent must be obtained.

By signing the informed consent form, the participant's legal guardian agrees that the participant will complete all evaluations required by the trial, unless the participant is withdrawn voluntarily or is terminated from the trial for any reason.

12.1 Assent Process (e.g., Minor)

When a study includes participants who may be enrolled in the study only with the consent of the participant's legally acceptable representative (e.g., minors), the participant should be informed about the study to the extent compatible with the participant's understanding. If capable, the participant should assent and sign and personally date the IRB-approved written assent form (if applicable based on local IRB guidelines). The assent form describes (in simplified terms) the details of the study, study procedures, and risks. Assent forms do not substitute for the consent form signed by the participant's legal guardian. Consult with the institution's policies regarding enrollment of participants who are unable to provide informed consent for themselves.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record participant data. The CRF will be used for the recording of all historical participant information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator. Data collection forms will be derived from the CRFs and provided by the DCC.

According to ICH E6, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file (regulatory binder) at the site is maintained. The study file will contain, but will not be limited to:

- Current package inserts and all previous versions
- Final study protocol
- Protocol amendments (if applicable)
- MOP (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists,

pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

DCC-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the principal investigator, Pediatric Trials Network, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 50, 45 CFR 46 and 21 CFR 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

15.2 Institutional Review Board

This protocol is to be reviewed in accordance with subpart D of 45 CFR 46. Prior to its implementation, this protocol, including any subsequent amendments, the informed consent form, assent form, and any materials or advertisements presented to participants, must be approved by an IRB constituted according to FDA regulations 21 CFR 56.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial, and a copy will be provided to the DCC. Notification of the IRB's composition and the institution's federal-wide assurance number will be provided to the DCC.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

15.3 Informed Consent

The investigator will choose participants in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, a participant's parent/legal guardian will provide informed consent for study enrollment. All participants' parents/legal guardians must provide informed consent based on consent form that complies with the requirements of both 21 CFR 50 and HIPAA before the participant enters the trial. A consent form that complies with the requirements of 21 CFR 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the participant's protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see **Section 12**.

15.4 Participant Confidentiality

Participants will be assigned unique code numbers and will not be identified by name. Participant confidentiality is held strictly in trust by the participating investigators, their staff, the sponsor(s), and their agents. This confidentiality extends to biological sample tests, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Clinical study sites will permit access to such records.

15.5 Study Discontinuation

If the study is discontinued, enrolled participants will continue to be followed for safety assessments for 3 days following the last dose of study drug, unless there is an ongoing SAE for which the participant will be followed for up to 10 days after the last dose of study drug.

16 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of serious adverse events, if required, and all IND safety reports.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the CRFs and provided by the DCC to the sites to record and maintain data for each participant enrolled in the study that is not otherwise captured in the medical record. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the CRF should be consistent with the source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the source documents and CRFs.

16.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team in real time. The site data entry staff will ensure that they are accurate and complete, and should enter the data into AdvantageEDC^{SM} within 72 business hours of data acquisition. Serious adverse events must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee in real time, and entered into AdvantageEDC^{SM} within 24 hours of identification. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

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

16.2 Data Capture Methods

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

16.3 Types of Data

Data for this study will include demographic data, medical history, physical examination data including height/weight/BMI, safety, laboratory, and outcome measures including PK data.

16.4 Timing/Reports

The DMC will convene and make recommendations on study continuation based on the safety data collected quarterly.

16.5 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the Investigator for 10 years after the end of the study or per local/state regulations or until participants reach 21 years of age, whichever is longer. Study information in a participant's medical records will be retained forever. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the PI when documents are no longer required to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1 and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor via the DCC's AdvantageEDC^{SM}.

A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB per their guidelines. The site principal investigator/study staff are responsible for knowing and adhering to their IRB requirements.

16.7 Participant Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 PUBLICATION POLICY

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

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

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND holder to register this trial in an acceptable registry.

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

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research.

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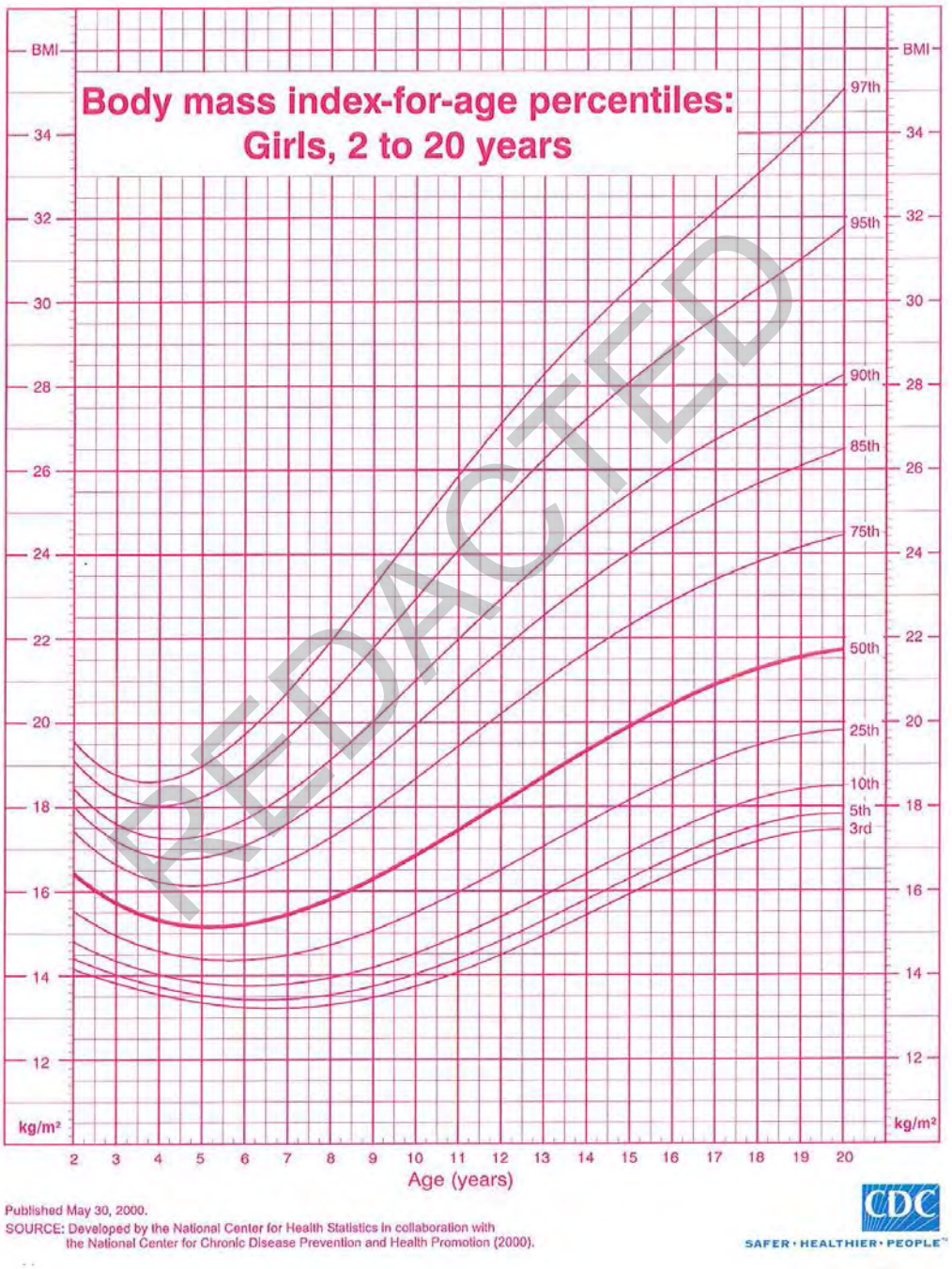
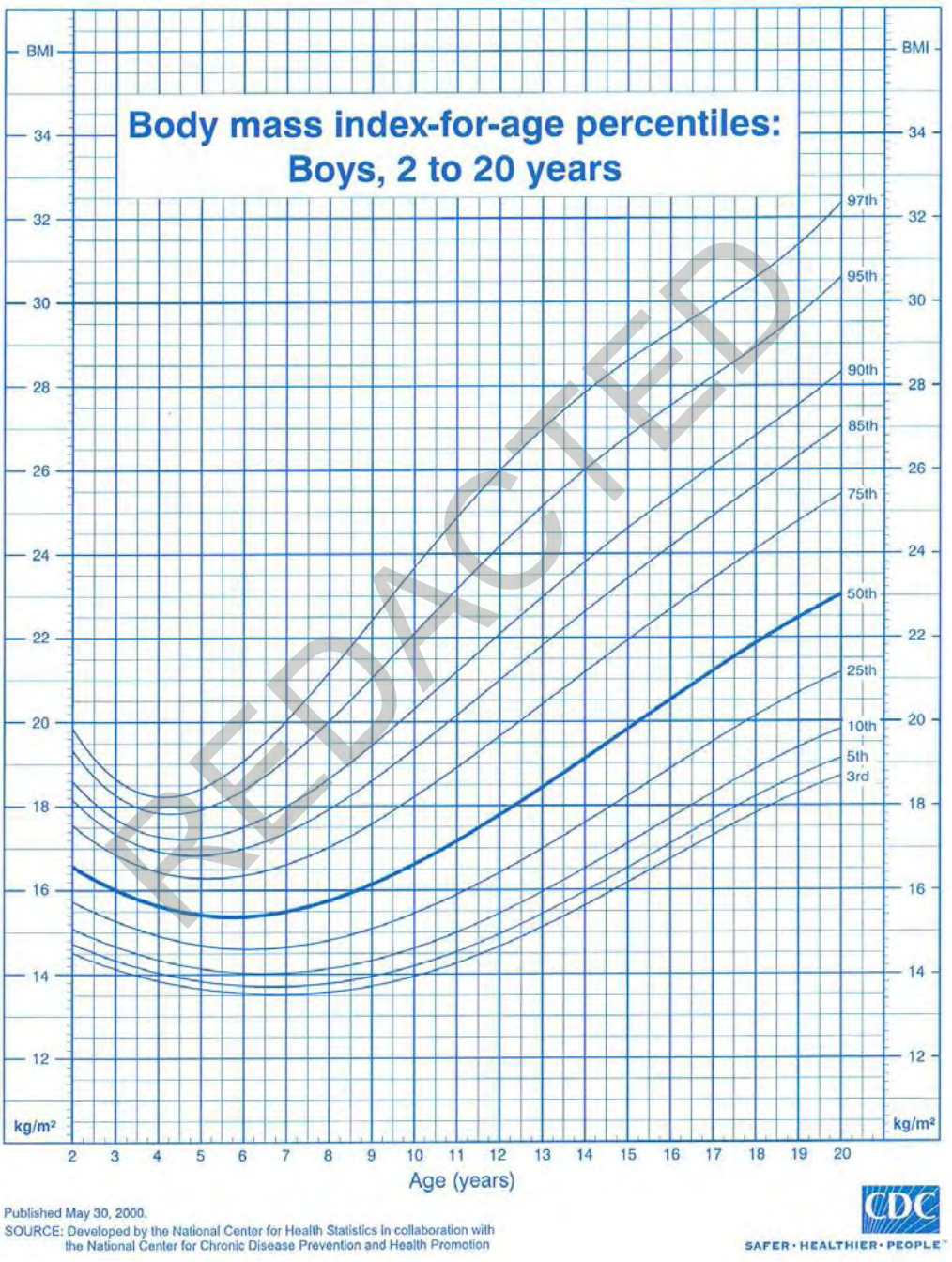
APPENDIX I: CDC MALE AND FEMALE CHILD BMI PERCENTILE CHARTS



APPENDIX I: CDC MALE AND FEMALE CHILD BMI PERCENTILE CHARTS (continued)



APPENDIX II: MEDICATIONS OF INTEREST

A. Exclusion for ALL participants at the time of enrollment:

1) CYP 3A4 potent inhibitors including:
   a. Cyclosporine
   b. Erythromycin, clarithromycin
   c. Itraconazole, ketoconazole
   d. Ritonavir, delavirdine, protease inhibitors
   e. Nefazodone, fluoxetine, fluvoxamine
   f. Verapamil and diltiazem
2) CYP 3A4 inducers
   a. Rifampin,
   b. Phenytoin
   c. Ritonavir
3) Other: St. John's Wart

B. Exclusion at the time of enrollment (unless the participant was receiving these drugs prior to enrollment AND was receiving clindamycin as part of routine care prior to enrollment):

1) Neuromuscular blocking agents: Clindamycin may enhance neuromuscular blocking effect.
   a. Atracurium
   b. Cisatracurium
   c. Pancuronium
   d. Rocuronium
   e. Succinylcholine
   f. Vecuronium

The above drugs are only excluded at the time of enrollment; if a participant begins taking any of the drugs while on-study, he/she will not be discontinued.

APPENDIX III: CAPSULE DOSING TABLES

WT_Low	WT_High		mg/kg/day_low	mg/kg/day_high	Goal	Total Daily Dose
20	20	150/150/150/150	30.0	30.0	30 mg/kg/day	600
21	30	300/300/300	30.0	42.9	30 mg/kg/day	900
31	40	300/300/300/300	30.0	38.7	30 mg/kg/day	1200
41	45	450/450/450	30.0	32.9	30 mg/kg/day	1350
46	60	450/450/450/450	30.0	39.1	30 mg/kg/day	1800
61	72	750/750/750	31.3	36.9	30 mg/kg/day	2250
73	80 >81	600/600/600/600 900/900/900	30.0	32.9	30 mg/kg/day	2400 2700
20	25	300/300/300	36.0	45.0	40 mg/kg/day	900
26	32	300/300/300/300	37.5	46.2	40 mg/kg/day	1200
33	38	450/450/450	35.5	40.9	40 mg/kg/day	1350
39	48	450/450/450/450	37.5	46.2	40 mg/kg/day	1800
49	56	750/750/750	40.2	45.9	40 mg/kg/day	2250
57	64 >64	600/600/600/600 900/900/900	37.5	42.1	40 mg/kg/day	2400 2700

APPENDIX IV: CLINDAMYCIN IN NON-OBESE CHILDREN

Ref	*PO clindamycin:*			*Dose 1*		*Dose 13*	*Dose 17*		
	Dose Amount	Age range (years)	*No. Subjects*	C_{max} (1 hour) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{min} (6 hours) (mcg/mL)	C_{max} (1 hour) (mcg/mL)	Half-life (h)	AUC (mcg/mL * h)
14	2 mg/kg	7-12	11	1.24 (0.70)	0.19 (0.27)	0.72 (0.21)	2.46 (0.68)	1.51 (0.74)	4.64 (2.11)
14	3 mg/kg	6-12	11	2.25 (0.53)	0.44 (0.19)	1.23 (0.31)	2.98 (0.93)	1.98 (0.60)	9.28 (2.71)
14	4 mg/kg	8-14	10	2.44 (0.65)	0.51 (0.25)	1.45 (0.36)	3.79 (0.61)	2.22 (0.78)	9.35 (3.23)
14	2 mg/kg	3-7	13	1.22 (0.51)	0.18 (0.23)	0.55 (0.17)	2.21 (0.51)	-	-
14	2 mg/kg	0.5-2	8	1.22 (1.14)	0.30 (0.37)	0.60 (0.32)	2.53 (0.86)	-	-
	IV clindamycin:			*Dose 1*					
				C_{max}	Half-life (h)				
5	5-7mg/kg	Pediatric patients”		10	2.5				

* All values are means (standard deviation).

C_{max} – maximum concentration; C_{min} – minimum concentration; AUC – area under the concentration time curve.