CLINICAL STUDY PROTOCOL

Study Title:	An Open-Label Study of the Pharmacokinetics of a Single Dose of Telavancin in Pediatric Subjects Aged 12 months to 17 Years
Study Short Title:	Telavancin Pediatric PK Study (Ages > 12 months to 17 Years)
Sponsor Study No.:	0101
ClinicalTrials.gov No.:	NCT02013141
Date:	26 August 2019, Amendment 5 31 January 2019, Amendment 4 20 September 2016, Amendment 3, Version 1.0 25 August 2015, Amendment 2 18 April 2014, Amendment 1 04 December 2013, Original Protocol
Test Product:	Telavancin
US IND:	[REDACTED]
Sponsor:	Cumberland Pharmaceuticals Inc. 2525 West End Avenue, Suite 950 Nashville, TN 37203 USA

This study will be conducted according to the principles of Good Clinical Practice.

PROTOCOL SYNOPSIS

Study Number and Title: Study 0101: An Open-Label Study of the Pharmacokinetics of a Single Dose of Telavancin in Pediatric Subjects Aged > 12 months to 17 Years

Study Short Title: Telavancin Pediatric PK Study (Ages > 12 months to 17 Years)

Estimated Number of Study Centers and Countries or Regions: At approximately 10 sites in the United States (US)

Background and Rationale:
Telavancin is a rapidly bactericidal, injectable antibiotic with concentration-dependent activity against clinically important Gram-positive pathogens. Telavancin is approved in the US for treatment, in adults, of complicated skin and skin structure infections and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*. This study is designed to evaluate the single-dose pharmacokinetics (PK) of telavancin in pediatric subjects to support development of a dosing algorithm that will deliver exposures similar to those found to be safe and effective in adults.

The most common adverse events, which occurred in ≥10% of telavancin-treated patients in Phase 3 studies of complicated skin and skin structure infections (cSSSI), were taste disturbance, nausea, headache, vomiting, foamy urine, and insomnia. In these studies, telavancin was compared in a blinded manner to vancomycin. Serious adverse events were reported in 7% of patients treated with telavancin, and the most common included renal, respiratory, and cardiac events. Treatment discontinuations due to adverse events occurred in 8% of patients treated with telavancin, the most common events being nausea and rash. The incidence of adverse events indicative of renal impairment (increased serum creatinine, renal insufficiency, and renal failure) was 3% of telavancin-treated patients, and serious adverse events indicative of renal impairment occurred in 1% of telavancin-treated patients.

Telavancin has also been evaluated in two Phase 3 trials in adults for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, again in a blinded comparison with vancomycin. Serious adverse events were reported in 31% of patients treated with telavancin. Treatment discontinuations due to adverse events occurred in 8% of patients who received telavancin, with the most common events being acute renal failure and QTc interval prolongation. Treatment-emergent adverse events reported in 5% or more of telavancin-treated patients included nausea, vomiting, and acute renal failure. The incidence of adverse events indicative of renal impairment (acute renal failure and increased serum creatinine) was 10% of telavancin-treated patients, and serious adverse events indicative of renal impairment occurred in 2% of telavancin-treated patients.

Telavancin has linear, predictable PK in the adult population. Mean plasma clearance after multiple dosing of 10 mg/kg every 24 hours in adults is 13.1 mL/hr/kg; the mean volume of distribution at steady state is 133 mL/kg, and the mean elimination half-life is 8.1 hours. Approximately 90% of telavancin is bound to plasma proteins, primarily albumin. Telavancin is predominantly eliminated renally, with approximately 60% of the dose excreted unchanged in urine over 48 hours.

PROTOCOL SYNOPSIS (CONTINUED)

Objectives:

Primary:

- To characterize the pharmacokinetics of telavancin after a single dose in pediatric subjects (>12 months to 17 years inclusive) who require systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection

Secondary:

- To assess the safety and tolerability of telavancin after a single dose in pediatric subjects (> 12 months to 17 years inclusive) who require systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection

Study Design: This is a multicenter, open-label, single-dose pharmacokinetic (PK) study. Infants, children, and adolescents will receive a single dose of telavancin infused intravenously (IV) over approximately 60 minutes.

Duration of Study Participation: Up to 9 days

Number of Subjects per Group:

In total, approximately 30 male and female infants, children, and adolescents will be enrolled into the study, as follows:

1. Adolescents (12 to 17 years), N = 8
2. Older Children (6 to 11 years), N = 8
3. Younger Children (2 to 5 years), N = 8
4. Infants >12 and < 24 months, N = 6

Cohorts 1, 2, 3 and 4 will be enrolled in parallel (simultaneously).

Study Population:

Male or female infants, children, and adolescents (> 12 months to 17 years, inclusive) who require systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection.

Inclusion Criteria:

Subjects who meet all of the following criteria will be eligible for study enrollment:

1. Subject is > 12 months to 17 years of age (inclusive)
2. Subject's weight is within the 3rd to 97th percentile (inclusive) for age and sex. Refer to Appendix 1 through Appendix 4.
3. Written informed consent and assent (if appropriate for older age groups) has been obtained per institutional review board (IRB) policy and requirements, consistent with ICH guidelines.
4. Male and female subjects of reproductive potential (i.e., post-pubertal males and post-menarche females) must agree to use a highly effective method of contraception

PROTOCOL SYNOPSIS (CONTINUED)

throughout study period and for 30 days after administration of study drug. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide; or intrauterine device (IUD) with documented failure rate of <1% per year; or oral/injectable/implanted hormonal contraceptives used in combination with an additional double-barrier method; or sexual abstinence.

5. Female subjects who are post menarche are required to have a negative serum pregnancy test before the administration of study drug.
6. Subject requires or recently completed systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection. If completed, the last administered dose of systemic antibiotic must be within 24 hours of enrollment.

Exclusion Criteria:

1. Subject has an estimated creatinine clearance <50 mL/min/1.73 m^2 (Schwartz equation).
2. Any clinically significant abnormal laboratory value, including hematology, chemistry, or urinalysis that in the judgement of the investigator would make it difficult to assess the pharmacokinetic profile and safety of a single dose of telavancin or would compromise the safety of the subject.
3. Any clinically significant medical history, abnormal physical examination finding, or vital sign measurement, including evidence of hemodynamic instability or significant collections of fluid outside normal vascular and tissue compartments (e.g., large pleural effusions, ascites), that in the judgement of the investigator would make it difficult to assess the pharmacokinetic profile or safety of a single dose of telavancin or would compromise the safety of the subject.
4. Subject has clinically relevant cardiac abnormality, in the opinion of the investigator, such as:
    a. A mean QTcF >440 msec, congenital long QT syndrome, second or third degree heart block at rest.
    b. Hemodynamically significant heart disease, eg, hemodynamically unstable congenital heart defect, uncompensated heart failure, uncorrected abnormal calcium, hyperkalemia, or any other unstable cardiac condition.
    c. An arrhythmic heart condition requiring medical therapy
5. Subject is receiving an anticoagulant AND requires specific coagulation testing (Prothrombin Time/International Normalized Ratio, Activated Partial Thromboplastin Time, Activated Clotting Time, or Coagulation Based Factor X Activity Assay) within 24 hours of receiving the telavancin dose. NOTE: Although telavancin does not interfere with coagulation, it interferes with some assays used to monitor coagulation.
6. Subjects who are receiving concomitant vancomycin treatment should not be assessed for vancomycin serum concentrations within 24 hours of receiving the Telavancin dose. NOTE: Telavancin might interfere with some Vancomycin therapeutic drug monitoring

PROTOCOL SYNOPSIS (CONTINUED)

assays. Caution should be exercised when interpreting vancomycin drug monitoring levels in the presence of telavancin.

7. Subject has a history of allergies or hypersensitivities to glycopeptide antibiotics (e.g., vancomycin), telavancin, or the formulation excipients.
8. Subject requires, or is anticipated to require, concomitant [within 24 hours before or 24 hours following the single dose of study medication (telavancin)] administration of agents that in the clinical judgment of the investigator increase the risk of torsade de pointes.
9. Subject is considered unlikely to comply with the study procedures.
10. Subject was treated with an investigational drug within 30 days or five half-lives, whichever is longer, before study entry.
11. Subject has any other condition that, in the opinion of an investigator, would confound or interfere with evaluation of safety of the investigational drug, or prevent compliance with the study protocol.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment: Telavancin 10 mg/kg will be administered as a single IV infusion over approximately 60 minutes to children in the 3 older age groups: Adolescents (12 to17 years), Older Children (6 to 11 years), Younger Children (2 to 5 years). The appropriateness of the dose(s) used in children > 12 months to < 24 months will be assessed during interim PK analyses of telavancin concentration-time data, including PK exposure estimates. The pediatric exposure estimates will be compared to historical data in adults to facilitate adjustment of the dose for the youngest age group. Pharmacokinetic results completed to date indicate that telavancin exposure is consistent with initial modeling projections; exposure was observed to decrease with decreasing body weight.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment: Not applicable

Study Evaluations

Safety Assessments:

Subject safety will be monitored during the study using standard measures, including physical examinations, vital signs, 12-lead ECGs, clinical laboratory assessments, urinalysis, concomitant medication usage, and adverse event reporting.

Pharmacokinetic Assessments:

Blood samples for PK assessment will be taken as follows: 1.0 hour (±5 min), 1.5 hours (±5 min), 2 hours (±5 min), 6 hours (±30 min), 12 hours (±30 min) and 24 hours (±30 minutes) after the beginning of the infusion. The timing of PK sampling may be optimized after the completion of the older age groups (Cohorts 1-3) to assure that the minimum numbers of samples are collected in the youngest age group > 12months to < 24 months. Plasma exposures that will be compared to adult exposures are the primary assessment for this study.

PROTOCOL SYNOPSIS (CONTINUED)

Plasma will be assayed for the determination of telavancin and the primary metabolite (AMI-11352).

Statistical Methods:

Sample Size:

The standard regulatory requirement for sample size in pediatric studies is to prospectively power to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance (CL_p) and volume of distribution (Vdss) in each pediatric age subgroup with at least 80% power.

Approximately 30 male and female infants, children, and adolescents will be enrolled into the study.

The subjects entered will be stratified by age:

- Adolescents (12 to 17 years), N= 8
- Older Children (6 to11 years), N = 8
- Younger Children (2 to 5 years), N = 8
- Infants > 12 and < 24 months, N = 6

Sample size for each pediatric age subgroup was determined on the basis of the variability in telavancin PK parameters from adult data.

Study Endpoints:

The primary study analysis variables are the telavancin PK parameters: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and $t_{1/2}$ (as appropriate) derived from plasma concentration-time data.

The secondary endpoints are safety variables (see Safety Assessments above).

Analysis:

Noncompartmental and/or population PK methods will be used for determination of plasma PK parameters. All PK parameters will be presented by individual listings and summary statistics according to age stratification, including mean, geometric mean, median, standard deviation, 95% confidence interval, and coefficients of variation, minimum, maximum and number of subjects. Further analyses of the potential relationship between PK parameters and subject age may be performed. Plasma concentration data may also be utilized for development of a pediatric population PK model.

Safety information gathered will be tabulated and descriptively summarized.

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Assessments

Procedure	Screening (Up to 48 Hours Before Dosing)	Day 1	Day 2	Follow Up (Day 8 ± 1 Day)[h]
Assent if appropriate and Informed Consent	X			
Review Inclusion/Exclusion Criteria	X	X		
Medication and Medical History	X			
Weight and Height/Length	X			
Vital Signs[a]	X	X	X	
ECG (12-lead)[b]	X	X		
Physical Examination	X			
Serum Pregnancy Test[c]	X			
Hematology, Serum Chemistry, Urinalysis[d]	X[d]		X[d]	
Telavancin Drug Dosing		X		
Plasma PK Sampling[e]		X	X	
Concomitant Medications	X	X	X	X[g]
Adverse Events	X	X	X	X[g]

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetic

a Vital signs (Heart rate [HR], blood pressure [BP], respiratory rate [RR] and body temperature) will be measured following dosing as outlined in Table 2. HR and BP will be measured after a subject has rested for at least 5 minutes in the seated or supine position.

b ECGs (12-lead) will be recorded after a subject has rested for at least 10 minutes in the supine position. If the screening ECG is collected less than 24 hours before study drug dosing, the ECG prior to dosing may be omitted. The ECG on Day 1 may be collected between 1.5 and 2.5 hours (±10 minutes) after commencement of the telavancin infusion.

c Pregnancy tests will be performed on female patients who are post menarche.

d If standard clinical laboratory tests have been performed within the protocol-specified windows for laboratory testing at screening and Day 2, the results may be used to avoid excessive blood draws. Only hematology and chemistry laboratory testing is required on Day 2.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

e Blood samples for plasma PK analysis of telavancin will be collected as outlined in Table 2.

f May be either an office visit or a telephone call, at the Investigator's discretion.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 2: Schedule of Procedures and Blood PK Collections

Sample or Procedure	Sampling Time Points (hours) relative to the start of the infusion					
	1.0[b]	1.5[b]	2[b]	6[b]	12[b]	24[b]
Heart Rate and Blood Pressure[a]	X[c]					X
Respiratory Rate and Temperature[a]	X[c]					X
Pharmacokinetic Sampling (Blood)	X[c]	X	X	X	X	X

a Heart rate [HR], blood pressure [BP], respiratory rate [RR] and body temperature will be measured after a subject has rested for at least 5 minutes in the seated or supine position.

b Collect PK sample at 1, 1.5 and 2 h (±5 minutes) and samples at 6, 12, and 24 h (±30 minutes).

c To be collected relative to the start of the infusion

Note: For procedures scheduled to be performed at common times, priority is to be given to collection of the PK samples at the designated time.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
A_e	amount excreted
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from time zero to the last measurable concentration
AUC_{0-inf}	area under the concentration-time curve from time zero extrapolated to infinity
BMI	body mass index
BP	blood pressure
BSA	body surface area
BSV	between-subject variability
CFR	(United States) Code of Federal Regulations
CDC	Centers for Disease Control and Prevention
CL_p	plasma clearance
CL_r	renal clearance
C_{max}	maximum concentration
CrCL	creatinine clearance
CRF	case report form
cSSSI	complicated skin and skin structure infection(s)
cSSTI	complicated skin and soft tissue infection(s)
ECG	Electrocardiogram
EDC	electronic data capture
Fe	fraction excreted
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	Intravenous

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
QTcF	Fridericia-Corrected QT Interval
REB	Research Ethics Board
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SDRC	Safety Data Review Committee
SOP	standard operating procedure
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time of maximum concentration
US	United States
VABP	ventilator-associated bacterial pneumonia
V_d	volume of distribution
Vd_{ss}	volume of distribution at steady-state

1 INTRODUCTION

1.1 Background and Rationale

Telavancin is a rapidly bactericidal, injectable antibiotic with concentration-dependent activity against clinically important Gram-positive pathogens. Telavancin is approved in the United States (US) for treatment, in adults, of complicated skin and skin structure infections and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*.

The most common adverse events (AEs), which occurred in ≥10% of telavancin-treated patients in Phase 3 studies of complicated skin and skin structure infections (cSSSI) were taste disturbance, nausea, headache, vomiting, foamy urine, and insomnia. In these studies, telavancin was compared in a blinded manner to vancomycin. Serious adverse events (SAEs) were reported in 7% of patients treated with telavancin, and the most common included renal, respiratory, and cardiac events. Treatment discontinuations due to adverse events occurred in 8% of patients treated with telavancin, the most common events being nausea and rash. The incidence of adverse events indicative of renal impairment (increased serum creatinine, renal insufficiency, and renal failure) was 3% of telavancin-treated patients, and serious adverse events indicative of renal impairment occurred in 1% of telavancin-treated patients.

Telavancin has also been evaluated in two Phase 3 trials for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, again in a blinded comparison with vancomycin. Serious adverse events were reported in 31% of patients treated with telavancin. Treatment discontinuations due to adverse events occurred in 8% of patients who received telavancin, with the most common events being acute renal failure and corrected QT (QTc) interval prolongation. Treatment-emergent adverse events (TEAEs) reported in 5% or more of telavancin-treated patients included nausea, vomiting, and acute renal failure. The incidence of adverse events indicative of renal impairment (acute renal failure and increased serum creatinine) was 10% of telavancin-treated patients, and serious adverse events indicative of renal impairment occurred in 2% of telavancin-treated patients.

Telavancin has linear, predictable PK in the adult population. Mean plasma clearance after multiple dosing of 10 mg/kg every 24 hours in adults is 13.1 mL/hr/kg; the mean volume of distribution at steady state is 133 mL/kg, and the mean elimination half-life is 8.1 hours.

Approximately 90% of telavancin is bound to plasma proteins, primarily albumin. Telavancin is predominantly eliminated renally, with approximately 60% of the dose excreted unchanged in urine over 48 hours.

This study is designed to evaluate the single-dose PK of telavancin in pediatric subjects to support development of a dosing algorithm that will deliver exposures similar to those found to be safe and effective in adults.

1.2 Nonclinical Profile

A review of the nonclinical profile of telavancin can be found in the current version of the telavancin Investigator's Brochure (IB).

1.2.1 Pharmacology

The summary of pharmacology data can be found in the current version of the telavancin IB.

1.2.2 Toxicology

The summary of toxicology data can be found in the current version of the telavancin IB. Studies in juvenile rats demonstrated that adverse effects and doses at which these effects were observed were similar in adult and juvenile rats.

1.2.3 Pharmacokinetics

The pharmacokinetics, excretion, metabolism, and tissue distribution of telavancin has been studied in animals. Findings of note include linear kinetics, urinary excretion as the primary route of elimination and little or no in vitro metabolism.

Further information can be found in the telavancin IB.

1.3 Clinical Experience

Details of clinical data obtained from completed studies to date may be found in the telavancin IB.

The PK, safety, and tolerability of telavancin administered intravenously in humans have been evaluated in 14 Phase 1 studies. The 14 studies were conducted in 484 subjects, including 18 healthy elderly subjects, 16 subjects with moderate hepatic impairment, and 79 subjects with various degrees of renal impairment. In addition, two drug-interaction

studies, a thorough QTc study, a study of telavancin PK after intravenous administration of single and multiple doses to healthy Japanese and white subjects, and a metabolism and excretion study using [^{14}C] telavancin have been completed in healthy subjects.

The safety and efficacy of telavancin have been evaluated in two Phase 2 studies. In one study, 184 patients with cSSSI were exposed to telavancin and in another study, 29 patients with bacteremia were exposed to telavancin. The safety and efficacy of telavancin have also been evaluated in four Phase 3 studies with vancomycin as a comparator, in which a total of 929 patients with cSSSI and a total of 751 patients with hospital-acquired bacterial pneumonia (HABP) were exposed to telavancin.

1.4 Risks and Benefits

The efficacy of telavancin has been demonstrated in Phase 3 studies of adult patients suspected to be caused by Gram-positive bacterial pathogens, in which telavancin demonstrated noninferiority to vancomycin. Because the current study will be evaluating single doses of telavancin in this pediatric population, no benefits are anticipated.

In single-dose studies of telavancin, the following adverse events have been reported: taste disturbance, headache, pruritus/urticaria, flushing, red man syndrome, hypersensitivity, constipation, transient elevated coagulation parameters, injection site pain, nausea, foamy urine, fatigue, somnolence, vasovagal syncope, decreased serum potassium, increased serum lactic dehydrogenase, and QT prolongation.

In Phase 2 and Phase 3 studies in which multiple doses of telavancin were administered, the following adverse events were reported: infusion-related reactions, urticaria, rash, pruritus, dermatitis, red man syndrome, renal insufficiency, QTc prolongation, ototoxicity, superinfection, and antibiotic-associated colitis/ pseudomembranous colitis. Laboratory abnormalities included elevations in serum creatinine and urea. In addition, increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed infrequently with no evidence of a relationship to telavancin dose.

Telavancin may pose a risk to fetuses, based on nonclinical data, and should be avoided during pregnancy unless the potential benefit outweighs the potential risks.

C. difficile-associated colitis is a potential adverse reaction and should be considered in subjects with diarrhea subsequent to drug administration.

1.4.1 Red Man Syndrome

Administration of glycopeptide antibiotics like telavancin may be associated with histamine release during the infusion and for a limited period thereafter. The syndrome is more prominent when the infusion is rapid, hence the use of a 1-hour infusion in this study. In extreme cases (eg, clinically severe symptoms including, for example, dyspnea, or angioedema), antihistamines may be necessary to alleviate the symptoms of red man syndrome and should be available for such an occurrence. In most cases, symptoms resolve without treatment within 15 to 30 minutes of onset. Refer to the IB for further details.

1.4.2 Subjects of Childbearing Potential

Adverse developmental outcomes were observed in three animal species at clinically relevant telavancin doses. This raises concerns about potential adverse developmental outcomes in humans (Section 5.4 of VIBATIV® prescribing information). Thus, female subjects who are post menarche are required to have a negative serum pregnancy test before the administration of study drug (Section 4). Females who are post menarche should be apprised of the animal teratology findings observed with the administration of telavancin. Males should be apprised of the effects on sperm count, motility, and morphology that were noted in animals exposed to telavancin.

Females of childbearing potential (defined as females who are post menarche) and sexually active males participating in telavancin studies must agree to use appropriate contraceptive measures for at least 30 days after the single dose of telavancin. Medically acceptable contraceptives include surgical sterilization; approved hormonal contraceptives (i.e., birth control pills, Depo-Provera®, or Lupron Depot®); barrier methods (i.e., condom, diaphragm) used with a spermicide; or an intrauterine device. Abstinence is a valid form of contraception. Study participants should be advised to inform the study physician immediately if they become pregnant, or their partner becomes pregnant, while participating in the study.

2 OBJECTIVES

The primary objective of the study is as follows:

- To characterize the pharmacokinetics of telavancin after a single dose in pediatric subjects (> 12 months to 17 years inclusive) who require systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection

The secondary objective of the study is as follows:

- To assess the safety and tolerability of telavancin after a single dose in pediatric subjects (> 12 months to 17 years inclusive) who require systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection

3 STUDY DESIGN

3.1 Overview

This is an open-label study of the pharmacokinetics and safety of a single intravenous dose of telavancin in pediatric subjects, aged > 12 months to 17 years, who require systemic antibiotic therapy or prophylaxis for a known or suspected bacterial infection. Pediatric subjects will be enrolled by age as follows:

1. Adolescents (12 to 17 years)
2. Older Children (6 to11 years)
3. Younger Children (2 to 5 years)
4. Infants (>12 and < 24 months)

Subjects' age will be based on their last birthday.

- Approximately eight subjects will be enrolled in Cohorts 1, 2 and 3 and approximately 6 subjects will be enrolled in Cohort 4. All 4 cohorts will be enrolled in parallel (simultaneously). The first eight (8) subjects (Cohort 1) will receive a single 10 mg/kg dose of IV administered telavancin. After the enrollment of the first 8 subjects and respective data are available, the population PK model will be refined and estimates of telavancin PK exposure will be generated for each subject. These estimates will then be compared to those observed historically in adults to facilitate adjustment of the pediatric dosing strategy, as necessary. PK data in patients recruited to date indicate that exposure to telavancin is consistent with initial modeling analysis and decreases with decreasing body weight. Therefore, the current dose is not expected to result in increased exposure in younger subjects with lower body weights. The Safety Data Review Committee (SDRC, Section 6.5) will make an integrated assessment of the safety, tolerability and available PK data after enrollment of approximately every 8 subjects for Cohorts 1-3 and after approximately 6 subjects for Cohort 4. .

Once a subject meets protocol eligibility, a single intravenous dose of telavancin will be administered over approximately 60 minutes on Day 1. Subjects will be followed for 24 hours for PK and safety assessments and will complete the study after a safety follow-up evaluation on Day 8 (± 1 day).

3.2 Rationale for Study Design

This study is designed as a multicenter, open-label study to evaluate the single-dose PK and safety of telavancin in pediatric subjects (> 12 months to 17 years). Because the primary objective of this study is characterization of PK, it has been designed as an open-label study. Approximately 30 male and female infants, children and adolescents will be enrolled. A single dose of 10 mg/kg has been selected for the first eight subjects in this study because it is the dose that has been previously evaluated and demonstrated to be safe and efficacious in adult patients.

In adults, telavancin exhibits a linear and predictable PK profile. The elimination $t_{1/2}$ of telavancin in adults with normal renal function is approximately 8.1 hours. PK measurements in this initial pediatric study will be assessed over 24 hours to ensure adequate characterization of the plasma PK profile in this population while minimizing unnecessary blood collections and hospitalization on the part of the subjects.

In adults, telavancin is primarily eliminated unchanged in the urine. Urinary excretion and the renal clearance of telavancin in the pediatric population will be assessed over 24 hours. Pediatric patients with estimated creatinine clearance <50 mL/min/1.73 m^2 will be excluded from the trial.

3.3 Selection of Dose and Duration of Treatment

Infants, children, and adolescents will receive a single intravenous (IV) telavancin dose infused over approximately 60 minutes. The initial starting dose of 10 mg/kg for the first eight subjects is the approved dose for treatment of complicated skin and skin structure infections (cSSSI) and treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus* in adult patients with creatinine clearance >50 mL/min.

Dose selection for the current study was based upon the current approved dose in adults (10 mg/kg), preclinical data, and simulations of the anticipated plasma exposure to telavancin in pediatric patients based on the adult telavancin population PK model and allometric scaling of telavancin clearance and volume of distribution to pediatric patients.

The effect of telavancin was evaluated in juvenile rats in a repeated-dose toxicity study. Based on these results, the effects of telavancin on juvenile animals did not differ

substantively from the effects in adults. A summary of the juvenile toxicology data may be found in the current version of the telavancin IB.

Clearance and volume of distribution were scaled allometrically from the adult population PK model across the pediatric age and weight range on the basis of an assumed allometric exponent of 0.75 (clearance) and 1.0 (volume of distribution), respectively.

Pediatric PK simulations were conducted utilizing a uniform distribution of body weights between 9.6 kg (average weight of a 1-year old child, based on WHO growth standards) and 70 kg. The distribution of creatinine clearance (CrCL) values was taken from the observed distribution of subjects in the adult population PK model and constrained to ≥50 mL/min in accordance with the study protocol. The age of each subject in the simulations was estimated by utilizing the average weight vs. age from the Centers of Disease Control and Prevention (CDC) growth charts for children in the United States {3}. Additionally, the values of CrCL for subjects 1 to 2 years of age were reduced by 15% to reflect dependence of renal function on size, organ maturation, and body composition {4}.

PK simulations for a pediatric dataset of 1500 subjects (n = 200 simulations per subject) and dose of 10 mg/kg were conducted using the population PK model and categorized by the age stratification that is defined in the protocol (Table 3). The mean and standard deviation of exposures (area under the curve [AUC]) in the pediatric population are anticipated to be lower than the 864 ± 285 µg•hr/mL observed at day 4 in the Phase 3 adult population (Studies 0015, 0017, 0018, and 0019) after a dose of 10 mg/kg (18 to 65 years of age, n = 393).

The selected dose level (10 mg/kg) is therefore anticipated to maintain plasma exposure to telavancin at comparable or lower levels than previously observed in the adult population. The results of this study will be utilized to design dosing algorithms in pediatric patients intended to maintain comparable exposures to the approved dose in adults. The appropriateness of the 10 mg/kg dose will be evaluated after enrollment of Cohorts 1-4.

Table 3: Exposures to Telavancin Based on a Population Pharmacokinetic Model in Pediatric (Predicted) and Adult (Actual) Subjects

Age Range	Estimated AUC_{0-24} (µg•hr/mL) (Mean ± SD)
Adult*	864 ± 285*
12 – 17 years	628 ± 214
6 – 11 years	537 ± 185
2 – 5 years	457 ± 160
1 – 2 years	433 ± 155

* Observed exposure on day 4 from Phase 3 clinical data (n = 393)

Note: Simulations based on a total of 300,000 simulated subjects at a telavancin dose of 10 mg/kg

3.4 Study Endpoints

The primary study analysis variables are the plasma PK parameters for telavancin. The following will be derived from plasma concentration-time data:

- Maximum observed plasma concentration (C_{max})
- Time to reach maximum observed plasma concentration (T_{max})
- Area under the plasma concentration versus time curve from time 0 to the last sample with measurable analyte concentration (AUC_{0-t})
- Area under the concentration versus time curve extrapolated to infinity (AUC_{0-inf})
- Terminal elimination half-life ($t_{1/2}$)

The secondary endpoints are safety and tolerability which will be monitored during the study using standard measures including physical exams, vital signs, 12-lead ECGs, clinical laboratory assessments, urinalysis, concomitant medication usage and adverse event monitoring (Safety Assessments, Section 6.4.3). An exploratory endpoint is the qualitative assessment of plasma concentrations for the metabolite AMI-11352.

3.5 Minimization of Bias

Since the primary objective of this study is characterization of PK, an open-label design is deemed appropriate.

3.5.1 Blinding

This is an open-label study.

3.5.2 Treatment Assignment

All subjects will receive a single dose of telavancin. See Section 5.2 for information regarding dose administration.

4 STUDY POPULATION

Approximately 30 male and female infant, child, and adolescent subjects' ages > 12 months to 17 years, inclusive, who require systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection will be enrolled in this study. Subjects will be enrolled by age into one of four subgroups:

1. Adolescents (12 to 17 years), N = 8
2. Older Children (6 to 11 years), N = 8
3. Younger Children (2 to 5 years), N = 8
4. Infants >12 and < 24 months, N = 6

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for study enrollment:

1. Subject is > 12 months to 17 years (inclusive)
2. Subject has a weight within the 3rd to 97th percentile (inclusive) for age and sex. Refer to Appendix 1 through Appendix 4.
3. Written informed consent and assent (if appropriate for older age groups) has been obtained per institutional review board (IRB) policy and requirements, consistent with ICH guidelines.
4. Male and female subjects of reproductive potential (ie, post-pubertal males and post-menarche females) must agree to use a highly effective method of contraception throughout study period and for 30 days after administration of study drug. A highly effective method of birth control is defined as one that results in a low failure rate (ie, <1% per year) when used consistently and correctly, such as condom + diaphragm, condom + spermicide, diaphragm + spermicide; or intrauterine device (IUD) with documented failure rate of <1% per year; or oral/injectable/implanted hormonal contraceptives used in combination with an additional double-barrier method; or sexual abstinence.
5. Female subjects who are post menarche are required to have a negative serum pregnancy test before the administration of study drug.
6. Subject requires or recently completed systemic antibiotic therapy for the treatment or prevention of a known or suspected bacterial infection. If completed, the last administered dose of systemic antibiotic must be within 24 hours of enrollment.

4.2 Exclusion Criteria

Subjects who satisfy any of the following criteria are not eligible for study enrollment:

1. Subject has an estimated creatinine clearance <50 mL/min/1.73 m^2 (Schwartz equation).
2. Any clinically significant abnormal laboratory value, including hematology, chemistry, or urinalysis that in the judgement of the investigator would make it difficult to assess the pharmacokinetic profile and safety of a single dose of telavancin or would compromise the safety of the subject.

3. Any clinically significant medical history, abnormal physical examination finding, or vital sign measurement, including evidence of hemodynamic instability, that in the judgement of the investigator would make it difficult to assess the pharmacokinetic profile or safety of a single dose of telavancin or would compromise the safety of the subject.
4. Subject has clinically relevant cardiac abnormality, in the opinion of the investigator, such as:
    a. A mean QTcF >440 msec, congenital long QT syndrome, second or third degree heart block at rest.
    b. Hemodynamically significant heart disease, eg, hemodynamically unstable congenital heart defect, uncompensated heart failure, uncorrected abnormal calcium, hyperkalemia, or any other unstable cardiac condition
    c. An arrhythmic heart condition requiring medical therapy
5. Subject is receiving an anticoagulant AND requires specific coagulation testing (Prothrombin Time/International Normalized Ratio, Activated Partial Thromboplastin Time, Activated Clotting Time, or Coagulation Based Factor X Activity Assay) within 24 hours of receiving the Telavancin dose. NOTE: Although Telavancin does not interfere with coagulation, it interferes with some assays used to monitor coagulation.
6. Subject is receiving concomitant vancomycin treatment AND requires vancomycin drug monitoring levels within 24 hours of receiving the Telavancin dose. NOTE: Telavancin might interfere with some Vancomycin therapeutic drug monitoring assays. Caution should be exercised when interpreting vancomycin drug monitoring levels in the presence of telavancin. NOTE: A subject who is receiving concomitant vancomycin and does not require vancomycin monitoring within the specified window would be eligible for enrollment.
7. Subject has a history of allergies or hypersensitivities to glycopeptide antibiotics (eg, vancomycin), telavancin, or the formulation excipients.
8. Subject requires, or is anticipated to require, concomitant (within 24 hours before or 24 hours following telavancin administration, administration of agents that are associated with torsade de pointes.
9. Subject is considered unlikely to comply with the study procedures.
10. Subject was treated with an investigational drug within 30 days or five half-lives, whichever is longer, before study entry.
11. Subject has any other condition that, in the opinion of an investigator, would confound or interfere with evaluation of safety of the investigational drug, or prevent compliance with the study protocol.

5 STUDY DRUGS

All study drug supplied by the Sponsor must be stored in a secure location accessible only to designated study personnel.

5.1 Description of Study Drug

Telavancin drug substance is manufactured as telavancin hydrochloride and is marketed as VIBATIV®. Telavancin hydrochloride is a lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. Telavancin is supplied in single-use vials containing 750 mg telavancin as a sterile, preservative-free lyophilized powder. Inactive ingredients are hydroxypropylbetadex, mannitol, and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment.

Telavancin is to be stored at refrigerated temperatures of 2°C to 8°C (35°F to 46°F). Excursions to room temperatures (up to 25°C [77°F]) for up to 7 days are acceptable.

Refer to the telavancin pharmacy manual for details on handling, reconstitution, dilution, and administration.

5.2 Dosage and Administration

Telavancin will be administered by qualified study site personnel as a single IV infusion using an IV pump over approximately 60 minutes. Telavancin may be administered without regard to meals. The first eight (8) subjects will receive a single dose of telavancin (10 mg/kg). The appropriateness of the 10 mg/kg dose will be evaluated after completion of a total of approximately 8, 16, 24, and 30 subjects in Cohorts 1- 4 using PK methods as described in Section 3.1.

The start time, stop time, and rate of each infusion will be recorded in the source documents for all subjects. Should red man syndrome (Section 1.4.1) occur in association with the infusion, the infusion should be stopped and not resumed. If the infusion is stopped for any reason, the following must be recorded in the source documents: the reason for stopping the infusion, the stop time of the infusion, and the rate of infusion just prior to being stopped. These data will be used to calculate the total amount of telavancin infused into the subject. All remaining study procedures should be completed for the subject.

5.3 Treatment Compliance

Subjects will receive a single IV dose of telavancin administered by qualified study personnel at the study site. Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug. Any discrepancies will be reviewed with the site staff and retraining on proper dosing will occur as needed.

5.4 Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all study drug(s) received from the Sponsor, in accordance with applicable government regulations and study procedures. The accountability records for study medication (telavancin) will be maintained in a secure location, accessible only to authorized staff members. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s).

Unused and expired study drugs will be disposed of in accordance with written instructions from the Sponsor. Copies of the study medication accountability records will be provided to the Sponsor at completion of the study and will be made available for review by the site monitor during the course of the study.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1 and Table 2.

6.2 Total Blood Volume

The total volume of blood to be drawn from each subject for PK and safety laboratory assessments is approximately 15 mL for females who are post menarche and 14.0 mL for males and pre-menarchal females as outlined in Appendix 7. Additional safety laboratory tests may be drawn, as required for safety assessments. Exact volumes will depend on individual sample volumes required at each institution. Blood sample volume must not exceed 5% of total blood volume (TBV) over 24 hours and up to 10% of TBV over 8 weeks. The investigator must ensure that the total volume of blood drawn does not exceed 5% of total blood volume especially in the youngest cohort. References for safe limits for a maximum blood volume to be drawn can be found in Appendix 8.

6.3 Procedures by Visit

Written assent, if applicable, and written informed consent must be obtained before any protocol specific procedures are performed.

The site should make every effort to perform procedures at the scheduled times, and the actual time should be recorded in the source documents and case report forms. When multiple assessments are scheduled at the same nominal time, PK sample collections should occur as close as possible to the scheduled nominal time. ECGs and vital signs may be collected prior to the PK sample collection.

6.3.1 Screening

The screening visit will be performed within 48 hours before planned dosing. Screening activities will comprise the following:

- Written, signed, and dated informed consent must be obtained after the nature of the study has been explained to the legally authorized representative and subject, if applicable, and before any study procedures are performed. Where applicable, assent will also be obtained based on local IRB requirements.
- Review of inclusion and exclusion criteria (Subjects will be eligible for enrollment only if they meet all the inclusion and none of the exclusion criteria)
- Medication and medical history

- Height and weight
- Vital signs
  - Heart rate (HR) and blood pressure (BP)
  - Respiratory Rate (RR) and body temperature
- ECG (12-lead)
- Physical examination as outlined in Section 6.4.3.4
- Blood collection (NOTE: If standard clinical laboratory tests have been performed within the protocol-specified windows for laboratory testing at screening, the results may be used to avoid excessive blood draws.)
  - Hematology
  - Serum chemistry
  - Serum pregnancy test (for females who are post menarche)
- Urine collection for urinalysis
- Concomitant medications
- Adverse events

6.3.2 Day 1 (see Table 1)

The following procedures will be performed on Day 1:

Pre-Dose Procedures:

- Review of inclusion and exclusion criteria (Subjects will be eligible for enrollment only if they meet all the inclusion and none of the exclusion criteria)
- Vital signs
  - HR and BP
  - RR and body temperature
- ECG (12-lead), (if not done within the past 24 hours)

Dosing:

- Study medication (telavancin) dosing, IV over 60 minutes (± 5 minutes)

Post dose Procedures:

- Vital signs at 1 (± 20 minutes) and 4 hours (± 20 minutes) after the start of the telavancin infusion
  - HR and BP
  - RR and body temperature
- ECG (12-lead), to be recorded between 1.5 and 2.5 hours (± 10 minutes) after the start of the telavancin infusion
- Blood collection
  - PK samples will be collected at 1 hour (± 5 min), 1.5 hours (± 5 min), 2 hours (± 5 min), 6 hours (± 30 min), and 12 hours (± 30 min), after the start of the telavancin infusion
- Adverse events
- Concomitant medications

6.3.3 Day 2 (Day of Discharge)

The following procedures will be performed on Day 2:

- Vital signs at 24 hours (± 2 hours) after the start of the telavancin infusion
  - HR and BP at 24 hours (± 2 hours) after the start of the telavancin infusion
  - RR and body temperature
- Blood collection
  - PK samples will be collected at 24 hours (± 30 minutes) after the start of the telavancin infusion
  - Hematology and serum chemistry laboratory testing. (NOTE: If standard clinical laboratory tests have been performed within the protocol-specified windows for laboratory testing on Day 2 (same calendar day), the results may be used to avoid excessive blood draws.)
  - Adverse events
- Concomitant medications

6.3.4 Day 8 (±1 day)/Follow-Up

The following procedures will be performed at the Follow-Up (Day 8 ±1 day), which should occur 7 days after dosing. At the discretion of the Investigator, the Follow-Up Visit may be either a clinic visit or telephone call:

- Adverse events
- Concomitant medications

6.3.5 Study Termination

Study termination will be considered the date that the subject withdraws from or completes the study, even if that date does not correspond to a protocol-specific visit.

6.3.6 Pregnancy Reporting

Study participants should be advised to inform the study physician immediately if they become pregnant, or their partner becomes pregnant, while participating in the study (Section 1.4.2).

6.4 Description of Study Assessments

6.4.1 Demographic and Baseline Assessments

6.4.1.1 Demographic Information

Demographic information to be collected will include: date of birth, sex, race, and ethnicity.

6.4.1.2 Height and Weight Measurements

Height and weight will be measured and recorded as outlined in Table 1. The subject's weight must be within the 3rd and 97th percentile (inclusive) for age and sex. For subjects aged > 12 months to <24 months, the charts in Appendix 1 and Appendix 2 should be used. For subjects age 2 to 17 years, Appendix 3 and Appendix 4 should be used.

Height or length (in centimeters) and weight (in kilograms) should be measured with the subject's shoes off. The body weight from Screening will be used to calculate the telavancin dose.

6.4.2 Pharmacokinetic Assessments

Blood samples for plasma PK assessments will be collected and processed according to instructions specified in the Pharmacokinetic Sample Collection Manual separate from this document. The total blood volume for PK is discussed in Section 6.2 and is outlined in Appendix 7.

Blood samples for PK assessment will be collected as follows:

- After the start of infusion: 1.0 hour (±5 min), 1.5 hours (±5 min), 2 hours (±5 min), 6 hours (±30 min), 12 hours (±30 min), and 24 hours (±30 minutes after the beginning of the telavancin infusion.

The actual time of collection must be recorded for each sample. Note that the PK sampling scheme may be optimized after the completion of each interim analysis to assure that the minimum number of samples are used in each subsequent set of six or eight subjects.

Refer to the Pharmacokinetic Sample Collection Manual for specific information on the collection and processing of PK plasma samples.

6.4.3 Safety Assessments

6.4.3.1 Adverse Events

Adverse events (AEs) will be recorded from the time of consent through the follow-up visit for each subject. AEs may be observed by the site study personnel or spontaneously reported by the subject or reported in response to a standard question from site study personnel and include any protocol-related event.

6.4.3.2 Medical History

A complete medical history will be taken during the Screening Visit and will include evaluation for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, and genitourinary diseases, surgical history, or any other diseases or disorders. Medical events or conditions that arise or worsen in severity or frequency following telavancin administration will be recorded as a (Treatment Emergent Adverse Event) TEAE.

6.4.3.3 Medication History

All medications used within the past 30 days will be recorded.

6.4.3.4 Physical Examination

The physical examination at Screening will be performed by an appropriately qualified individual (e.g., physician or nurse practitioner or physician's assistant or equivalent under the supervision and/or delegation of a physician) and will include examination of the following: general appearance; head, ears, eyes, nose, and throat; neck, skin/dermatologic system; cardiovascular system; respiratory system; abdomen/gastrointestinal system; genitourinary system, lymphatic system; musculoskeletal system; and nervous system. Post screening examinations will be abbreviated and based on symptomatology, largely focused on evaluation of AEs, if any, and any abnormalities identified on the Screening examination.

6.4.3.5 Vital Signs

Heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature will be taken as outlined in Table 1 and Table 2.

Blood pressure and heart rate will be measured after the subject has been resting for at least 5 minutes in the seated or supine position. Blood pressure will be measured using a calibrated manual or automatic blood pressure device. Heart rate will be recorded by palpation of the radial pulse over a 60-second period or by the automated blood pressure device.

Body temperature will be measured (oral, tympanic, or axillary) using a digital thermometer and recorded in degrees Celsius.

Any screening or pre-dose vital sign outside the normal range may be repeated once at the discretion of the investigator.

6.4.3.6 Electrocardiograms

Twelve-lead ECGs will be collected at each scheduled time point as specified in the Table 1 after the subject has been resting in the supine position for at least 10 minutes. If the screening ECGs are collected less than 24 hours before study drug dosing, the ECG prior to dosing may be omitted.

6.4.3.7 Laboratory Tests

The following laboratory assessments will be performed as specified in Table 1 and Table 2. Refer to the Laboratory Manual for specific information on the collection and processing of laboratory tests.

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or adverse events during the study may be performed at the discretion of the Investigator or upon request of the Sponsor. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the Screening evaluation of the subject may be repeated once at the discretion of the Investigator.

All laboratory safety testing will be performed by the local laboratory. These local laboratory safety test results will be used to determine a subject's eligibility for entry into the study. Study specific lab results will be entered into the case report form. If standard clinical

laboratory tests have been performed within the protocol-specified windows for laboratory testing at screening or Day 2, the results may be used to avoid excessive blood draws.

6.4.3.7.1 Hematology

Hematology samples will be analyzed for the following: hematocrit and hemoglobin; red blood cell count; white blood cell count, including automatic differential count (percent and absolute) of neutrophils, eosinophils, basophils, monocytes, lymphocytes; mean corpuscular volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; and platelet count.

6.4.3.7.2 Serum Chemistry

Serum chemistry samples will be analyzed for the following: albumin, sodium, potassium, calcium, chloride, bicarbonate, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase.

6.4.3.7.3 Urinalysis

Urinalysis includes determination of pH; specific gravity; presence of blood, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, and leukocytes; and microscopic examination of sediment, if clinically indicated.

6.4.3.7.4 Pregnancy Tests

Serum β-human chorionic gonadotropin pregnancy tests will be performed for all females who are post menarche.

6.5 Safety Data Review Committee

A Safety Data Review Committee (SDRC) will be composed of internal Sponsor personnel only, including the Cumberland Clinical Study Director, the Medical Monitor, the statistician and the PK scientist. Additional members may be added as needed at the discretion of the Clinical Study Director.

An SDRC meeting will be held after the enrollment of approximately every 8 subjects for Cohorts 1-3 and after approximately 6 subjects for Cohort 4. Data from these subjects has to be completed and available before the meeting. The SDRC will also meet if a Stopping Rule is met (Table 4). Available safety data, including demographic data, ECG results, vital

signs, adverse events, and laboratory results, and any available PK data will be reviewed at each meeting. Additional meetings will be scheduled as needed to review safety and available PK data.

As enrollment in Cohorts 1, 2, 3 and 4 may be ongoing during the SDRC, the SDRC may recommend that the study continues without modification; dosing adjustments; a cohort be expanded; or that dosing be discontinued.

Table 4: Stopping Rules

Scenario	Action
Any occurrence of a suspected telavancin-related moderate adverse drug reaction of the same system class (eg, cardiovascular) observed in two or more subjects * Exception: red man syndrome, local site reactions,	• Stop dosing additional subjects and convene SDRC (if event occurs outside the regularly scheduled review). • Review AE and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. • Upon unanimous decision by the SDRC, one of the following decisions may be made: – Discontinue enrollment – Continue enrollment ** If moderate red man syndrome is observed in at least two subjects, then the rate of telavancin infusion will be decreased by 50% for subsequent subjects
Any occurrence of a suspected telavancin-related severe or serious adverse drug reaction	• Stop dosing additional subjects and convene SDRC (if event occurs outside the regularly scheduled SDRC). • Review AE and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. • If a severe or serious adverse event is determined by the SDRC to be related to study drug and clinically or medically significant, no further administration at this dose should occur. Enrollment of the study may continue at a lower dose upon unanimous decision of the SDRC.

6.6 Concomitant Medications

Concomitant use of other antibiotics for bacterial infections, prophylaxis, or empiric therapy for a suspected bacterial infection are allowed during the study.

Subjects cannot participate in the study if they are:

- Receiving concomitant vancomycin treatment AND require vancomycin drug monitoring levels within 24 hours of receiving the telavancin dose. NOTE: Telavancin might interfere with some Vancomycin therapeutic drug monitoring assays. Caution should be exercised when interpreting vancomycin drug monitoring levels in the presence of telavancin.

- Subject requires, or is anticipated to require, concomitant (within 24 hours before or 24 hours following telavancin administration), administration of agents that are associated with torsade de pointes.

Additional prescription and over-the-counter medications are permitted. Any addition or change in regimen of concomitant medications should be recorded in the source documents and the eCRF. Medications taken from 30 days before enrollment through Follow-Up should be recorded in the source documents and eCRF.

6.7 Discontinuation

6.7.1 Subject Discontinuation

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the early termination visit should be carried out. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject from the study or a subject may choose to terminate participation before completion of the study include, but are not limited to, the following:

- Adverse event
- Subject choice
- Major violation of the protocol
- Termination of the study by the Sponsor
- Other

Subjects who discontinue study drug early due to an adverse reaction or any other reason (other than withdrawal of consent) should be encouraged to continue their participation in the follow-up safety assessments. If a subject fails to return for scheduled visits, a documented effort (e.g., at least 2 phone calls to the subject and a certified letter) must be made to determine the reason.

6.7.2 Subject Replacement

Subjects who discontinue the study due to an AE will not be replaced. Subjects with serious protocol violations where PK is not evaluable will be replaced. Subjects discontinued for other reasons may be replaced at the Sponsor's discretion.

6.7.3 Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason.

6.8 Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study, the Sponsor clinical study director (or designee) must be notified immediately. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7 ADVERSE EVENTS

7.1 Regulatory Definition of an Adverse Event

In the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice, Section 1.2 defines an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.2 Adverse Event Definition for the Purposes of This Study

For the purposes of this the Sponsor clinical study, adverse events will be defined as follows:

An adverse event (AE) is any untoward medical occurrence in a subject who has signed an informed consent form and is participating in a clinical investigation. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered related to the study drug (investigational product).

Preexisting events that increase in frequency or severity or change in nature during or as a consequence of participation in clinical studies will also be considered as adverse events. An AE may also include pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF, if applicable for the study.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen

- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

7.3 Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the case report form, including the dates of onset and resolution, severity, relationship to study drug, outcome, and action taken with study medication.

Clinical severity should be recorded and graded using mild, moderate or severe as described below.

Mild	= Awareness of signs or symptoms, but easily tolerated
Moderate	= Discomfort sufficient to cause interference with usual activities
Severe	= Incapacitation with inability to work or perform usual activities

The relationship to study drug therapy should be assessed using the following definitions:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears **with some degree of certainty** to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)

- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse

Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. In reports of death due to disease progression, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

7.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [ECGs], X-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of

an adverse event (or serious adverse event), as described in Sections 7.2 (Adverse Event Definition for the Purposes of This Study) and 7.4 (Serious Adverse Events).

If there are any AE questions, the investigator is encouraged to contact the Sponsor clinical study director or medical monitor to discuss.

7.6 Serious Adverse Event Reporting

Any SAE that occurs after a subject signs an informed consent form through the follow-up visit (or at the time a subject is determined to be ineligible for the study or who does not enroll in the study), regardless of causal relationship, must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event.

To report an SAE, complete and fax the Serious Adverse Event Report Form to the following:

[REDACTED]

For medical questions regarding an SAE, contact the Sponsor medical monitor by telephone as follows:

[REDACTED]

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current Telavancin Investigator's Brochure. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.7 Adverse Event Follow-up

A subject experiencing an AE or SAE will be followed by the investigator or his/her trained delegate(s) through the follow-up visit or until the investigator and/or the Sponsor has determined that the AE or SAE has resolved or a stable clinical endpoint is reached,

whichever is longer. The Sponsor may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8 STATISTICAL CONSIDERATIONS

8.1 Analysis Objectives

The principal objectives of this study are to characterize the PK and assess the safety and tolerability of telavancin after a single dose in pediatric subjects (> 12 months to 17 years).

8.2 Sample Size and Power

The standard regulatory requirement for sample size in pediatric studies is to prospectively power to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance (CL_p) and the volume of distribution (Vdss) in each pediatric subgroup with at least 80% power.

Sample size for each pediatric age subgroup was determined on the basis of the variability in telavancin PK parameters from adult data. Data from all Phase 1 telavancin studies (eight studies, which included a total of 236 healthy subjects without infection) conducted by the Sponsor were used to estimate variability using two different methods (based on either a noncompartmental analysis or a population PK modeling approach), as outlined in Wang et al {1}. The corresponding sample size intended for PK analysis was calculated using the estimated variability.

1) Based on noncompartmental analysis: Determine variability from any prior relevant study by calculating the standard deviation (SD) of the natural log–transformed individual clearance (CL) and volume of distribution at steady state (Vd_{ss}). Noncompartmental analysis of data from the Phase 1 trials resulted in SDs of 0.27 and 0.21 for CL and Vd_{ss}, respectively.

2) Based on population PK modeling: Estimate the SD based upon the between-subject variability (BSV) found in the population PK model. The BSVs in the population PK model {2} were used, ie, 29% and 23% for CL and V1, respectively. The corresponding estimates of the SDs derived from the BSVs were 0.284 and 0.227 for CL and V1, respectively.

Using the most conservative estimate of SD (0.284 for CL derived from the population PK model), a sample size of seven per age subgroup is deemed sufficient to meet the aforementioned requirements with at least 80% power. In anticipation of possible drop-outs or missing samples, eight subjects will be enrolled in each age subgroup, which will result in

a total of approximately 30 male and female infants, children and adolescents participating in this study:

- Adolescents (12-17 years), N=8
- Older Children (6-11 years), N = 8
- Younger Children (2-5 years), N = 8
- Infants >12 and < 24 months, N = 6

8.3 Enrollment

This is an open-label study and parallel (simultaneous) enrollment is allowed for all Cohorts.

8.4 Endpoints

8.4.1 Safety Endpoints

Safety endpoints include adverse events, concomitant medications, laboratory measurements, ECGs, physical examinations, and vital signs.

8.4.2 Pharmacokinetic Endpoints

The primary study analysis variables are the telavancin PK parameters: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and $t_{1/2}$ (as appropriate) derived from the plasma concentration-time data.

8.5 Statistical Analysis

8.5.1 General Considerations

Unless otherwise specified, results will be tabulated and summarized descriptively; all individual subject data will be fully listed.

The number and percentage of patients will be presented for categorical variables while mean, median, standard deviation and range (minimum and maximum) will be presented for continuous variables.

The statistical package SAS (C

ary, North Carolina) will be used to produce summary tables and subject listings related to demographics, baseline characteristics, patient disposition and safety assessment.

8.5.2 Handling of Missing Data

Unless otherwise specified, missing values will not be imputed.

8.5.3 Analysis Populations

Two analysis populations will be defined:

- Safety population: all subjects who receive any amount of study drug.
- PK population: all subjects who receive any amount of study drug and who provide PK data from at least one post-dose plasma sample.

8.5.4 Demographics, Baseline Characteristics and Patient Disposition

Summary of demographics and baseline characteristics will include all subjects from the Safety population. The number of subjects discontinuing the study prematurely and the reason for discontinuing will be summarized based on the Safety population.

8.5.5 Safety

All safety assessments will be conducted on the Safety population.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset on or after initiation of study medication. The number and percentage of patients reporting TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA®, version 16 or a more recent version) system organ class and preferred term, severity, and relationship to study medication. Serious TEAEs and TEAEs resulting in discontinuation of study drug will be summarized separately.

Concomitant medications will be mapped using the WHODRUG dictionary (WHODDE B2 format, March 2013 or a more recent version). The number and percentage of patients taking each concomitant medication will be tabulated.

Analysis of laboratory results will be based on those reported by the local laboratory. Continuous laboratory measurements will be descriptively summarized at each visit for observed values and changes from baseline. Categorical laboratory measurements will be summarized by the number and percentage of patients with low, normal and high values based upon the normal ranges provided by each local laboratory. If a normal range is missing for a particular local laboratory then the normal “textbook range” will be used. A shift

table of laboratory measurements comparing pre- and post-treatment values relative to normal ranges (for example, normal to low, normal to normal, or normal to high) will also be summarized.

Vital signs and ECG parameters (based on average of multiple measurements if measured) will be summarized at each visit for observed values and changes from baseline. In addition, QT and QTc intervals will be summarized categorically as number and percentage of patients with abnormal values or increases.

8.5.6 Analysis of Pharmacokinetics

For all PK data analyses, the PK population will be used.

Individual and mean drug concentration versus time curves for telavancin and its metabolite, AMI-11352, will be presented by subgroup. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time point and pediatric age subgroup.

Plasma telavancin concentration-time data will be used to obtain T_{max}, C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$ (as appropriate).

Noncompartmental and/or population PK modeling methods will be used for determination of plasma PK parameters. All PK parameters will be presented by individual listings and summary statistics according to age stratification (e.g., mean, geometric mean, median, standard deviation, 95% confidence interval, coefficients of variation, minimum, maximum, and number of subjects). Further analysis of the potential relationship between PK parameters and subject age may be performed. Plasma concentration data may also be utilized for development of a pediatric population PK model.

In the first step of the population PK model development for this analysis, the full population PK model from adults will be modified to incorporate the expected alteration in renal function with age in the pediatric population {6}. This modified model will then be used to simulate expected telavancin concentration-time profiles in adolescent patients receiving the planned dose of 10 mg/kg in order to ensure that the resultant PK exposures (C_{max} and AUC) are consistent with those observed in adult patients administered telavancin in previous clinical studies. Once the study has begun enrollment, a modified population PK model will be fit to the telavancin plasma concentration-time data from the first set of eight subjects in order to

assess the applicability of the model and to verify that dosing of the next set of eight subjects at 10 mg/kg remains appropriate. Further modifications to the model will be made if an adequate fit to the data is not obtained using the previous population PK model. These may include: 1) changes to the residual error model; 2) addition or deletion of inter-individual variability terms; and/or 3) modifications to the covariate relationships. The basic structural model (2 compartments, linear elimination) will not be modified. This process will be repeated for each successive set of eight subjects by fitting the model to all of the available data from the study at the time of the interim analysis.

At study completion, the telavancin population PK model in children will be completed by fitting the model to the final, locked data from the protocol. In addition to confirming the covariate relationships identified in the iterative process described above, the model will be qualified using accepted pharmacometric techniques. The methods and results of the population PK analysis of data from this pediatric study will be reported separately from the clinical study report.

Preliminary metabolite profiling of plasma may be conducted.

8.6 Data Monitoring Committees

No data monitoring committee independent of the Sponsor is planned for this study. Refer to Section 6.5 for details regarding the Safety Data Review Committee comprised of internal Sponsor personnel only.

9 STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1 Principal Investigator Responsibilities

Before beginning the study, the principal investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A sub-investigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the Telavancin Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/Independent Ethics Committee (IEC) complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2 Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and Good Clinical Practice (GCP) requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by The Sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the Sponsor study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3 Informed Consent

A properly written and executed ICF, in compliance with-ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

For studies in which a legally authorized representative (LAR) provides informed consent on behalf of the subject, documentation will also be required to indicate the relationship of the LAR to the subject.

The investigator will provide copies of the signed ICF to each subject (or the subject's legally authorized representative) and will maintain the original in the subject's record file.

9.4 Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, eg, electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (eg, correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, ie, after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5 Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult the Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6 Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by

the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, ie, placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7 Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8 Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9 Publication

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between the Sponsor and the investigator.

10 REFERENCES

The following references are available upon request.

1. Wang Y, Jadhav PR, Lala M, Gobburu, JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol. 2012;52:1601-6.
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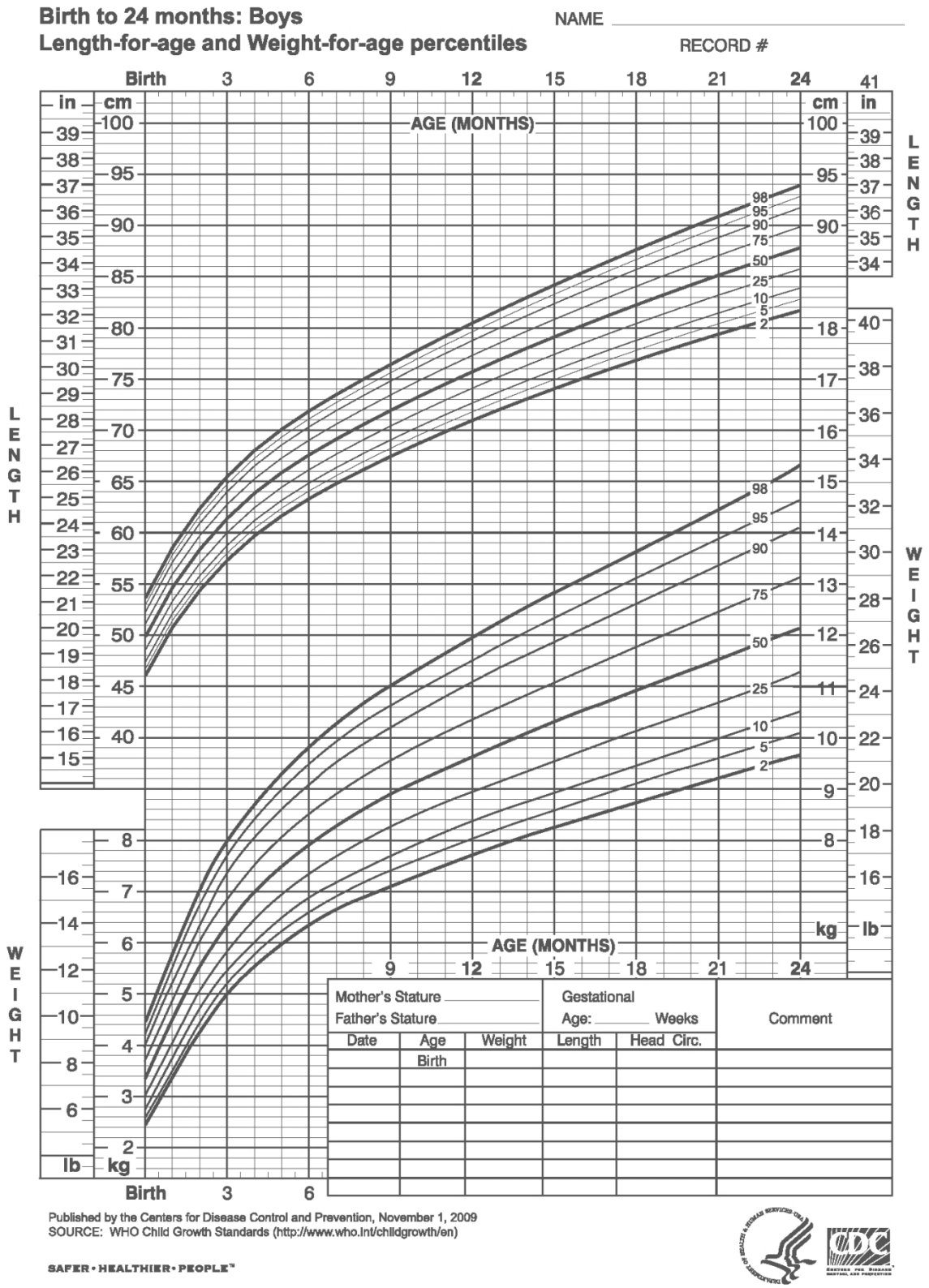
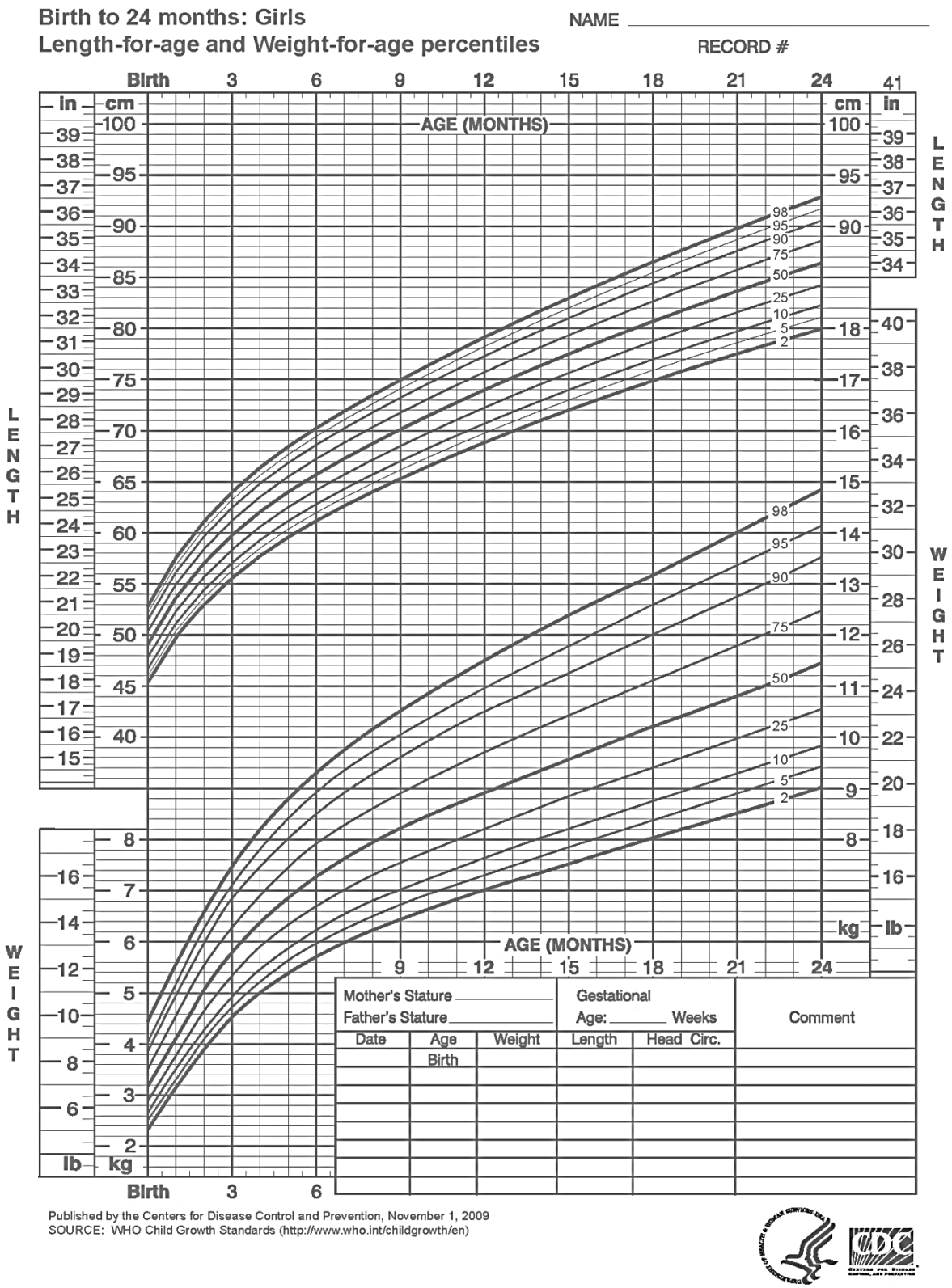
4. Holford N. Dosing in children. Clin Pharmacol Ther. 2010 Mar;87(3):367-70.
5. Beers, MH. The Merck Manual of Diagnosis and Therapy, Nineteenth Edition. The Merck Publishing Group, Rahway, NJ: Merck & Co, Inc., 2011.
6. Rhodin MM et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr. Nephrol. 24, 67–76 (2009
7. Schwartz G. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009 Nov;4(11):1832-43.
8. Sahai, J, Healy DP, Shelton MJ, Miller JS, Ruberg SJ, Polk R. Comparison of vancomycin and teicoplanin-induced histamine release and “red man syndrome”. Antimicrob. Agents Chemother. 1990, 34(5):765-9.

11 APPENDICES

Appendix 1: Growth Charts for Boys, Birth to 36 Months

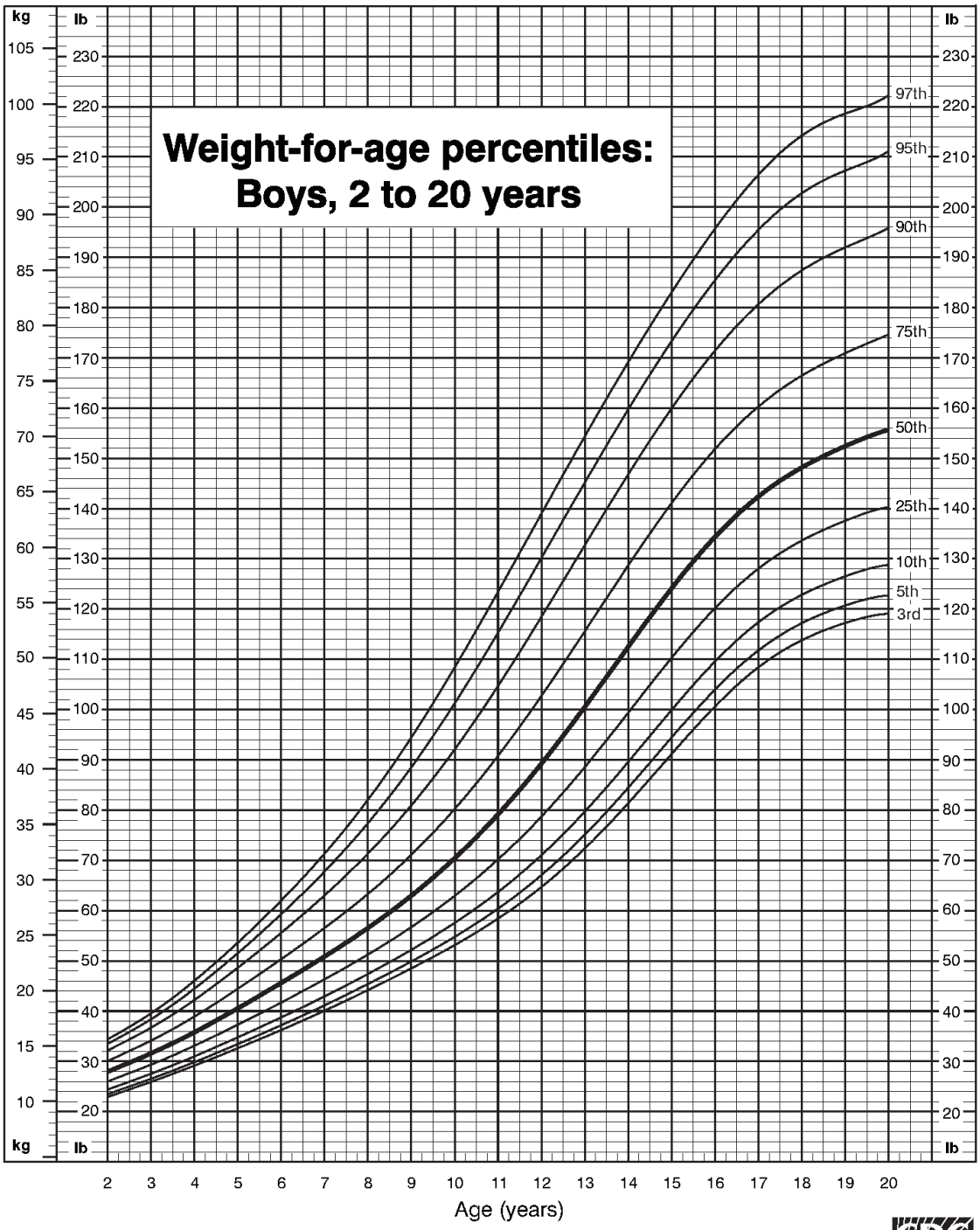


Appendix 2: Growth Charts for Girls, Birth to 36 Months



Appendix 3: Weight-for-Age Percentiles (5th to 95th Percentiles) for Boys, 2−20 Years

CDC Growth Charts: United States



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 (2000).

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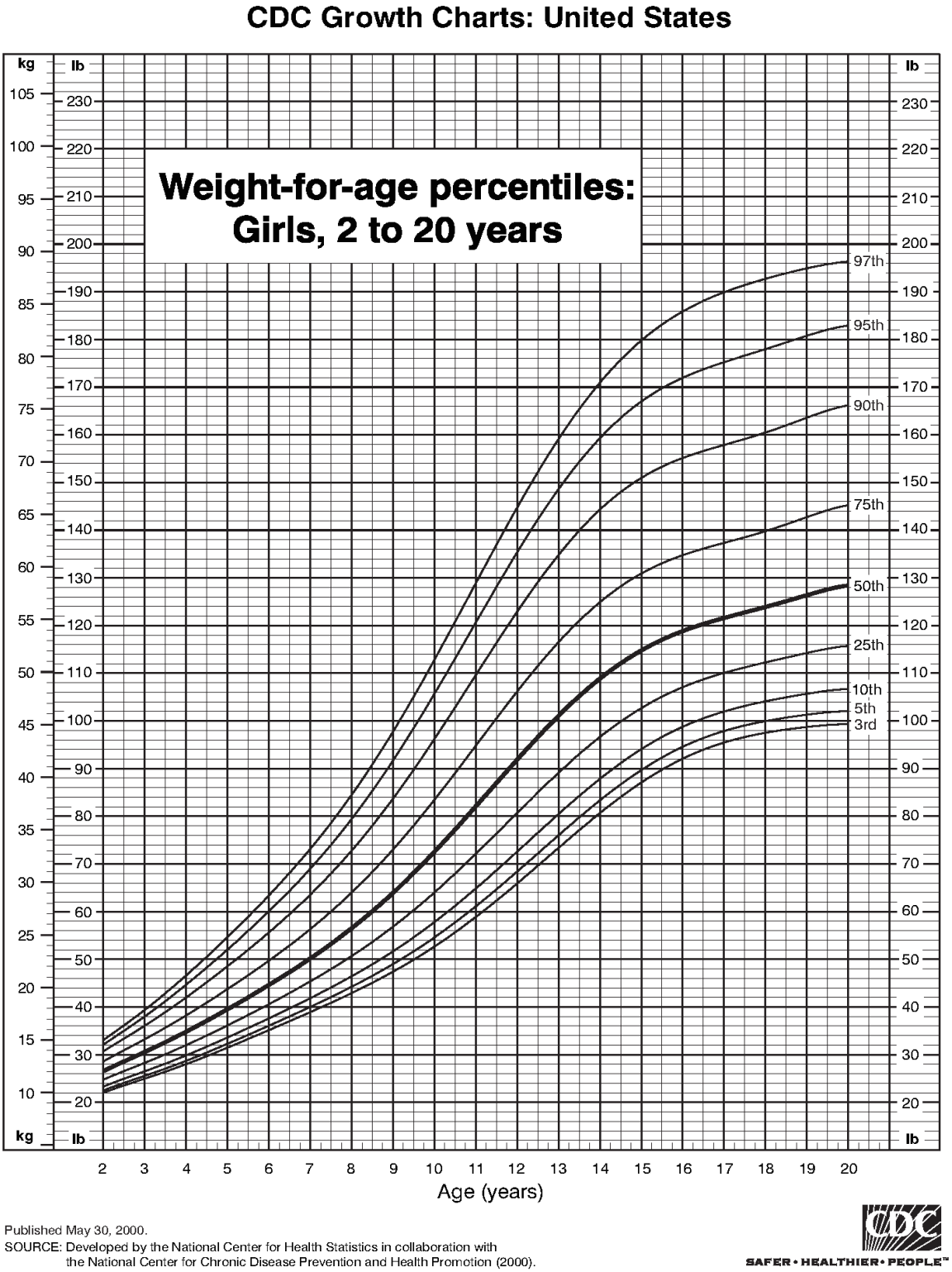
Appendix 4: Weight-for-Age Percentiles (5th to 95th Percentiles) for Girls, 2−20 Years



Appendix 5: Schwartz Equation for Estimated Creatinine Clearance

The estimated creatinine clearance will be calculated using the Schwartz equation {5, 7} as follows:

$$\text{creatinine clearance (mL/min/1.73m}^2\text{)} = \frac{k \times \text{height or length (in cm)}}{\text{serum creatinine (in mg/dL)}}$$

Where k = constant of proportionality that is age-specific:

k = 0.55 for subjects 1 to 12 years
k = 0.55 for female subjects >12 years
k = 0.70 for male subjects >12 years

Appendix 6: Severity Grading for Red Man Syndrome

	No Reaction	Mild	Moderate	Severe[a]
Erythema	0 (<1% BSA)	1 (1 - 5% BSA)	2 (5 - 10% BSA)	3 (>10% BSA)
Pruritus	0	1	2	3
Global Severity (Calculated from the sum of the individual scores for erythema and pruritus)	0	1-2	3-4	5-6

BSA – body surface area

a Red man syndrome may also meet severe criteria if muscle spasm, chest pain, dyspnea, or hypotension is present.

Source: Sahai, et al {7}

Appendix 7: Number of Samples and Approximate Amount of Blood to Be Collected from Each Subject

Blood Draws for Study 0101										
	Prestudy Screen	**Day 1**					**Day 2**	**Total # Blood Draws**	**Approximate blood Volume Per Draw[a] (mL)**	**Subtotal mL of Blood**
Hours post dose		1	1.5	2	6	12	24			
Pregnancy Test*	1							1	1	1
Hematology	1						1	2	2	4
Chemistry	1						1	2	3.5	7
Plasma PK		1	1	1	1	1	1	6	0.5	3
Total / study day	2-3*	5					3	8		
									Total volume needed (mL)	14.0-15.0 mL*[a]

* 1.0 mL required for those not requiring a pregnancy test; pregnancy test done only on females who have reached menarche

a. Actual blood volume will vary by institution, but will not exceed not exceed 5% of total blood volume (TBV) over 24 hours and up to 10% of TBV over 8 weeks (see Section 6.2).

Appendix 8: Maximum Allowable Total Blood Volumes to Be Collected from Each Subject

CMRC IRB MAXIMUM ALLOWABLE TOTAL BLOOD DRAW VOLUMES (CLINICAL + RESEARCH)						
Body Wt (Kg)	Body Wt (lbs)	Total blood volume (mL)	Maximum allowable volume (mL) in one blood draw (= 2.5% of total blood volume)	Total volume (clinical + research) maximum volume (mL) drawn in a 30-day period	Minimum Hgb required at time of blood draw	Minimum Hgb required at time of blood draw if subject has respiratory/CV compromise
1	2.2	100	2.5	5	7.0	9.0 -10.0
2	4.4	200	5	10	7.0	9.0-10.0
3	6.3	240	6	12	7.0	9.0-10.0
4	8.8	320	8	16	7.0	9.0-10.0
5	11	400	10	20	7.0	9.0-10.0
6	13.2	480	12	24	7.0	9.0-10.0
7	15.4	560	14	28	7.0	9.0-10.0
8	17.6	640	16	32	7.0	9.0-10.0
9	19.8	720	18	36	7.0	9.0-10.0
10	22	800	20	40	7.0	9.0-10.0
11-15	24-33	880-1200	22-30	44-60	7.0	9.0-10.0
16-20	35-44	1280-1600	32-40	64-80	7.0	9.0-10.0
21-25	46-55	1680-2000	42-50	64-100	7.0	9.0-10.0
26-30	57-66	2080-2400	52-60	104-120	7.0	9.0-10.0
31-35	68-77	2480-2800	62-70	124-140	7.0	9.0-10.0
36-40	79-88	2880-3200	72-80	144-160	7.0	9.0-10.0
41-45	90-99	3280-3600	82-90	164-180	7.0	9.0-10.0
46-50	101-110	3680-4000	92-100	184-200	7.0	9.0-10.0
51-55	112-121	4080-4400	102-110	204-220	7.0	9.0-10.0
56-60	123-132	4480-4800	112-120	224-240	7.0	9.0-10.0
61-65	134-143	4880-5200	122-130	244-260	7.0	9.0-10.0
68-70	145-154	5280-5600	132-140	264-280	7.0	9.0-10.0
71-75	156-185	5680-6000	142-150	284-300	7.0	9.0-10.0
76-80	167-176	6080-6400	152-160	304-360	7.0	9.0-10.0
81-85	178-187	6480-6800	162-170	324-340	7.0	9.0-10.0
86-90	189-198	6880-7200	172-180	344-360	7.0	9.0-10.0
91-95	200-209	7280-7600	182-190	364-380	7.0	9.0-10.0
96-100	211-220	7680-8000	192-200	384-400	7.0	9.0-10.0