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Study ID: DAL-MD-04

Title: A Phase 2, Single-center, Open-label, Randomized, Comparator-Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Patients with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms

Protocol Date: 23 Jun 2015

1.0

TITLE PAGE

**Durata Therapeutics International BV (an Affiliate of Actavis, Inc.)
Spaces Zuidas II
Barbara Strozziilaan 101, 1083HN, Amsterdam
The Netherlands**

**A Phase 2, Single-center, Open-label, Randomized, Comparator-Controlled Trial of
the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Patients
with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms**

DAL-MD-04

Dalbavancin

IND # 60,613

Original Protocol Date: 23 Jun 2015

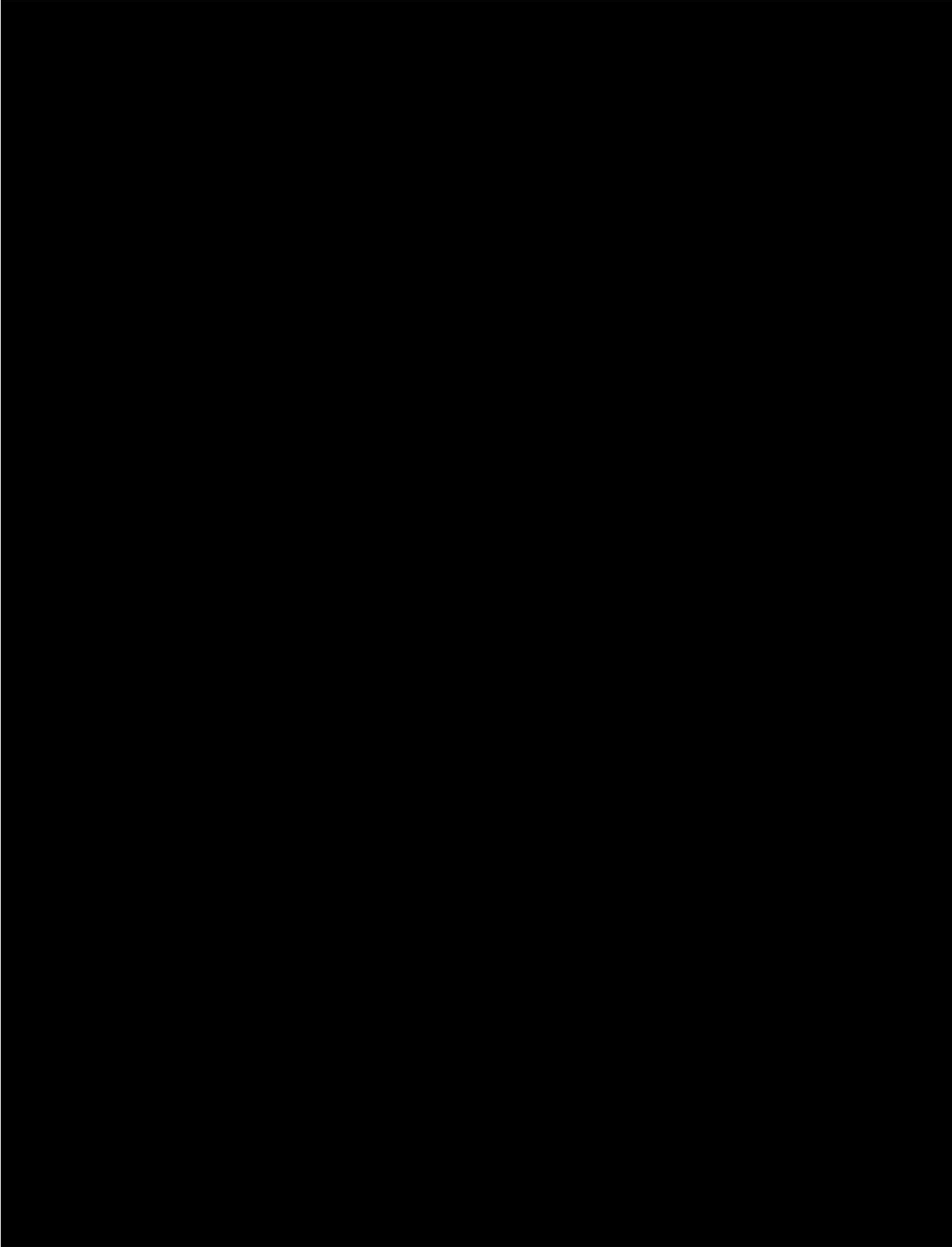
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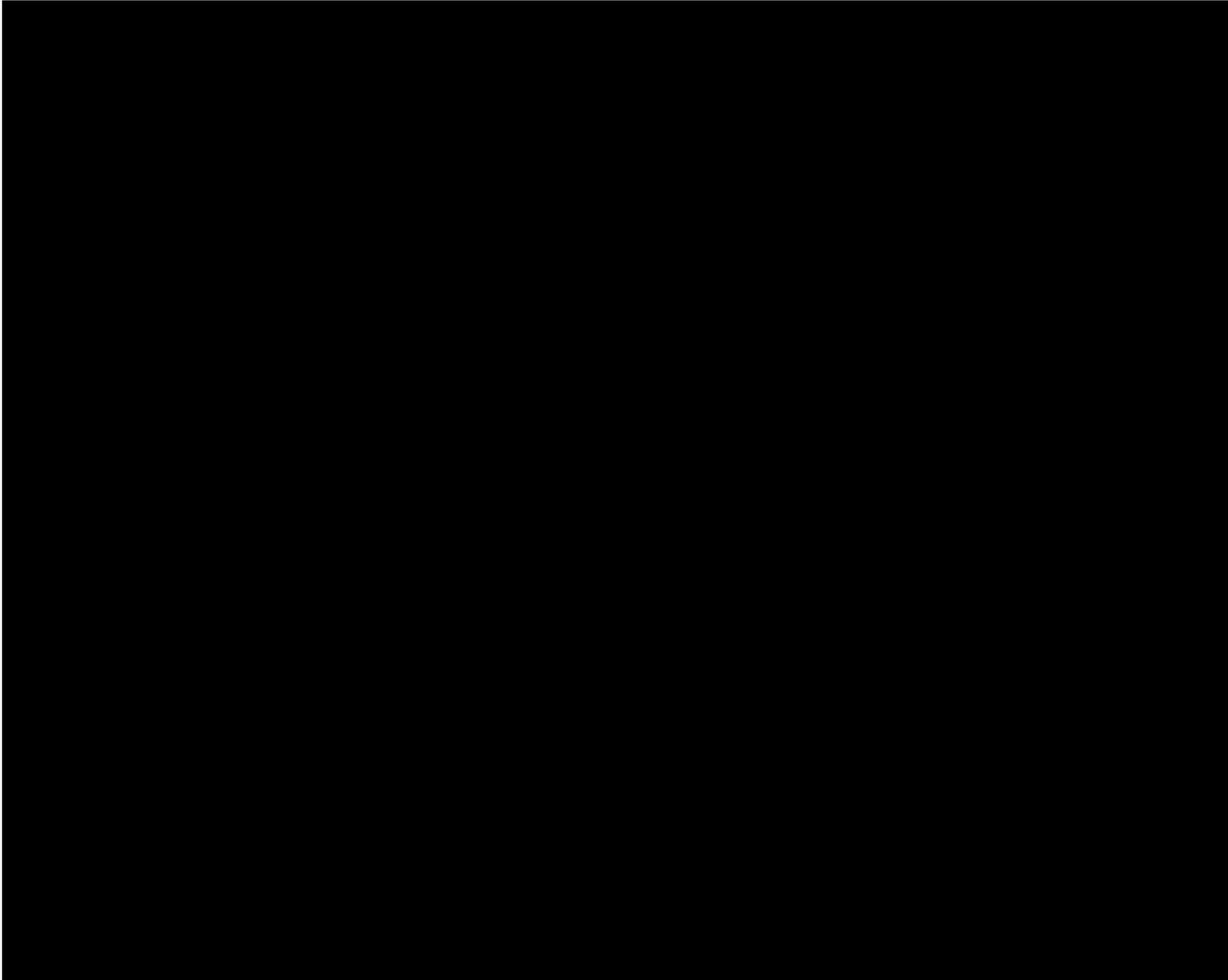
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2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study DAL-MD-04	
Title of Study	A Phase 2, Single-center, Open-label, Randomized, Comparator-controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Subjects with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms
Study Centers (Country)	1 (Ukraine)
Development Phase	2
Objectives	<p>Primary-</p> <ul style="list-style-type: none"> To determine the efficacy of dalbavancin for the treatment of the first episode of osteomyelitis known or suspected to be caused by Gram-positive pathogens in adults <p>Secondary-</p> <ul style="list-style-type: none"> To assess the safety and tolerability of dalbavancin in adult patients with osteomyelitis. To estimate clinical response rate per pathogen in the dalbavancin group at the end of therapy (Day 42) and Day 180 To estimate clinical response rate in the dalbavancin group at Day 21, Day 180 and Day 365 [REDACTED]
Methodology	Single-center, open-label, parallel-arm, randomized, efficacy and safety study
Number of Patients	Approximately 80 (70 in the dalbavancin treatment group and 10 in the comparator treatment group)
Diagnosis and Main Criteria for Inclusion	Male and female patients who are ≥ 18 years of age that meet the diagnostic criteria for osteomyelitis defined as pain or point tenderness upon palpation or probing to bone, and either radiological findings consistent with a diagnosis of osteomyelitis or a bone specimen with Gram-positive cocci on a baseline Gram-stain
Test Product, Dosage, and Mode of Administration	<p>Dalbavancin 1500 mg IV over 30 minutes on Day 1 and Day 8 (if creatinine clearance ≥ 30 mL/min or if on regular hemodialysis or peritoneal dialysis)</p> <ul style="list-style-type: none"> Dose reduction if creatinine clearance < 30 mL/min (and not receiving regular hemodialysis or peritoneal dialysis): Dalbavancin 1000 mg IV over 30 minutes on Day 1 and Day 8
Duration of Treatment	<p>Treatment: 2 doses of dalbavancin 1 week apart, 4-6 weeks comparator</p> <p>Follow up: 365 days from the start of therapy</p>
Reference Therapy, Dosage, and Mode of Administration	<p>Standard of care antibiotic (oral or intravenous) for the treatment of osteomyelitis based on the judgment of the study physician</p> <p>Drugs allowed as concomitant medications</p> <ul style="list-style-type: none"> Aztreonam may be administered at randomization for presumed co-infection with a Gram-negative pathogen and could be discontinued if a Gram-negative pathogen is not documented by culture results. A switch to an oral antibiotic for coverage of Gram-negative pathogens is allowed once evidence of clinical improvement has been established. Metronidazole (IV or oral) or oral vancomycin may be used for Clostridium difficile infections. Other antibiotics that do not achieve significant therapeutic concentrations in the serum (eg, nitrofurantoin) may be considered for treatment of other concomitant infections. Close consultation with the medical monitor is advised prior to use of these antibiotics. <p>Surgical debridement should be performed on any patient if clinically indicated.</p>

Criteria for Evaluation	
Primary Outcome Measure	Clinical response at Day 42 in the Clinically Evaluable (CE) population
Secondary Outcome Measures	<ul style="list-style-type: none"> • Clinical improvement at Day 21 in the mITT and CE Populations • Clinical response (cure, failure, or indeterminate) at Day 42 in the mITT and micro-mITT Populations • Clinical response (cure, failure, or indeterminate) at Day 180 in the mITT and CE Populations • Clinical response (cure, failure, or indeterminate) at Day 365 in the mITT and CE Populations • Clinical response (cure, failure, or indeterminate) by pathogen at Day 42 and Day 180 in the CE Population
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
Pharmacokinetic Measures	Not Applicable
Statistical Methods	<p>The study is exploratory in nature. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Listings of individual patient's data will be produced.</p> <p>[REDACTED]</p>





3.1 TABLE OF CONTENTS

	Page
1.0 TITLE PAGE	1
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS.....	2
3.0 TABLE OF CONTENTS AND TABLES	
3.1 TABLE OF CONTENTS.....	6
3.2 LIST OF IN-TEXT TABLES	12
4.0 LIST OF ABBREVIATIONS.....	13
5.0 ETHICAL CONSIDERATIONS.....	15
5.1 INDEPENDENT ETHICS COMMITTEE.....	15
5.2 ETHICAL CONDUCT OF THE STUDY.....	15
5.3 PATIENT INFORMATION AND INFORMED CONSENT.....	15
6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	16
7.0 INTRODUCTION	17
8.0 STUDY OBJECTIVES.....	20
9.0 INVESTIGATIONAL PLAN.....	21
9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION	21
9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS	21
9.3 SELECTION OF STUDY POPULATION.....	21
9.3.1 Inclusion Criteria.....	21
9.3.2 Exclusion Criteria.....	22

9.3.3 Removal of Patients From Therapy or Study Assessment.....	24
9.3.3.1 Premature Discontinuation From Study Drug	24
9.3.3.2 Withdrawal From Study.....	25
9.3.4 Patient Replacement Procedures	26
9.4 TREATMENTS.....	27
9.4.1 Treatments Administered	27
9.4.1.1 Dalbavancin Treatment Group.....	27
9.4.1.2 Standard of Care Treatment Group.....	27
9.4.1.3 Other Additional Antibacterial Therapy	27
9.4.1.4 Duration of Treatment.....	27
9.4.2 Identity of Investigational Products	28
9.4.3 Method of Assigning Patients to Treatment Groups.....	28
9.4.4 Selection of Dosages in the Study.....	29
9.4.4.1 Dose Adjustments - Dalbavancin.....	30
9.4.4.2 Dose Adjustments - Other Investigational Products.....	31
9.4.5 Blinding.....	31
9.4.6 Unblinding.....	31
9.4.7 Prior and Concomitant Therapy	32
9.4.8 Monitoring Treatment Compliance.....	32
9.5 EFFICACY AND SAFETY VARIABLES.....	33
9.5.1 Efficacy Assessments.....	33
9.5.1.1 Primary and Secondary Efficacy Assessments	33
9.5.1.1.1 Primary Efficacy Assessment.....	33

9.5.1.1.2 Secondary Efficacy Assessments	33
9.5.1.2 Microbiological Assessments	34
9.5.1.2.1 Blood Samples for Culture	34
9.5.2 Safety Assessments	34
9.5.2.1 Adverse Events	35
9.5.2.1.1 Abnormal Test Findings	36
9.5.2.2 Causality Assessment.....	37
9.5.2.3 Severity Assessment	38
9.5.2.4 Serious Adverse Events	38
9.5.2.4.1 Hospitalization.....	39
9.5.2.5 Reporting Adverse Events and Serious Adverse Events	40
9.5.2.6 Immediate Reporting of Serious Adverse Events and Events of Special Interest	41
9.5.2.7 Reporting of Pregnancies Occurring During the Study	42
9.5.2.8 Potential Hy’s Law Cases	42
9.5.2.9 Clinical Laboratory Determinations	43
9.5.2.9.1 Potential Drug-Induced Liver Injury/Hy’s Law	43
9.5.2.10 Vital Signs, Body Weight, and Height.....	44
9.5.2.11 Physical Examination.....	44
	44
	44
	45
	46

	47
	47
	48
	48
	49
	50
	50
9.6 DATA QUALITY ASSURANCE	51
9.6.1 Data Recording and Documentation	51
9.6.2 Data Monitoring	52
9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	52
9.7.1 Analysis Populations	52
9.7.1.1 Screened Population.....	52
9.7.1.2 Intent-to-Treat Population.....	52
9.7.1.3 Safety Population	52
9.7.1.4 Modified Intent-to-Treat Population.....	53
9.7.1.5 Clinically Evaluable Population	53
9.7.1.6 Microbiological mITT Population	53
9.7.2 Patient Disposition	53
9.7.3 Demographics and Other Baseline Characteristics	54
9.7.4 Extent of Exposure and Treatment Compliance	54
9.7.4.1 Extent of Exposure.....	54

9.7.4.2 Measurement of Treatment Compliance.....	55
9.7.5 Efficacy Analyses.....	55
9.7.5.1 Primary Efficacy Parameter.....	55
9.7.5.2 Secondary Efficacy Parameters	55
	56
9.7.6.1 Adverse Events	56
9.7.6.2 Clinical Laboratory Parameters	57
9.7.6.3 Vital Signs.....	58
	58
9.7.8 Interim Analysis	58
9.7.9 Determination of Sample Size.....	58
9.7.10 Computer Methods.....	58
9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES	59
9.9 PROTOCOL DEVIATIONS.....	59
10.0 STUDY SPONSORSHIP.....	60
10.1 STUDY TERMINATION	60
10.2 REPORTING AND PUBLICATION	60
11.0 INVESTIGATOR OBLIGATIONS	61
11.1 DOCUMENTATION	61
11.2 PERFORMANCE.....	61
11.3 USE OF INVESTIGATIONAL MATERIALS	62
11.4 CASE REPORT FORMS	62

11.5 RETENTION AND REVIEW OF RECORDS	62
11.6 PATIENT CONFIDENTIALITY	63
12.0 INVESTIGATOR’S STATEMENT	64
13.0 APPENDICES	65
APPENDIX I. ELEMENTS OF INFORMED CONSENT	65
[REDACTED]	67
APPENDIX III. POTENTIAL DRUG-INDUCED LIVER INJURY/HY’S LAW	68
[REDACTED]	70
14.0 LITERATURE CITED	72

3.2 LIST OF IN-TEXT TABLES

	Page
	
Table 9.4.4.1–1. Dalbavancin Dosage Adjustments for Renal Impairment	31

4.0

LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under curve
CA-MRSA	community-acquired methicillin-resistant <i>staphylococcus aureus</i>
CFR	Code of Federal Regulations
CFU	colony-forming units
CRP	C-reactive protein
cSSSI	complicated skin and skin structure infection
eCRF	electronic case report form
EDC	electronic data capture
EOIV	end of intravenous
ESR	erythrocyte sedimentation rate
FDA	US Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat

IV	intravenous, intravenously
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
MIC ₉₀	minimum inhibitory concentration 90
MITT	modified intent-to-treat
Micro-mITT	microbiological modified intent-to-treat
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
PCS	potentially clinically significant
PHL	potential Hy's Law
RSM	Regional Site Manager
SAE	serious adverse event
SOC	standard of care
TEAE	treatment-emergent adverse event
TOC	test-of-cure
ULN	upper limit of normal

5.0 **ETHICAL CONSIDERATIONS**

5.1 INDEPENDENT ETHICS COMMITTEE

This study will be carried out in full compliance with the guidelines of the independent ethics committee (IEC) and government agencies of the Ukraine as well as the European Union Clinical Trial Directive (Directive 2001/20/EC), where applicable. Before the study begins, the site will require approval from an IEC and government agency. During the course of the study, the Sponsor or authorized representative will provide timely and accurate reports to the IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IEC of SAEs or other significant safety findings. The study protocol, Informed Consent Form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IEC at the study site in conformance with CFR, Title 21, Part 56, the European Union Clinical Trial Directive (Directive 2001/20/EC), and local regulations.

5.2 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and Good Clinical Practice (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the CFR.

5.3 PATIENT INFORMATION AND INFORMED CONSENT

Patients, after being given an explanation of the study, will give voluntary and written informed consent before participating in any study-related procedures.

Each patient (or his or her legally authorized representative) will read, assent to an understanding of, and sign an instrument of ICF after having had an opportunity to discuss it with the study staff before signing; each patient will be made aware that he or she may withdraw from the study at any time.

The informed consent statement contains all the elements of informed consent listed in [Appendix I](#) of this protocol. Signed copies of the ICF will be given to the patient, and both documents will be placed in the Investigator's study files.

6.0 **INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

This study will be performed at 1 study center in the Ukraine.

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator must meet his or her obligations to the patients, ethics committee, Sponsor, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of their capabilities and performance consistent with the study investigational plan. The Investigator will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IEC, and completing the electronic case report forms (eCRFs).

7.0 **INTRODUCTION**

Osteomyelitis is an infection of bone that can occur as a result of hematogenous seeding (transmitted via blood), contiguous spread of infection to bone from adjacent soft tissues and joints (eg, cellulitis, septic arthritis), or direct inoculation of infection into the bone as a result of trauma or surgery (Fritz and McDonald, 2008). Hematogenous osteomyelitis is usually monomicrobial, while osteomyelitis due to contiguous spread or direct inoculation is usually polymicrobial. *Staphylococcus aureus* (*S. aureus*) is the organism most commonly isolated from all forms of osteomyelitis (Calhoun et al, 2009).

Standard treatment for osteomyelitis requires prolonged antibiotic therapy (4-6 weeks) and may require surgical debridement (removal of infected tissue). Whenever possible, antibiotic therapy should be tailored to culture and susceptibility findings. Antimicrobials with activity against the most commonly isolated organism, *S. aureus*, are routinely used. These include anti-staphylococcal penicillins (nafcillin/oxacillin), clindamycin, first-generation cephalosporins (cefazolin), and vancomycin. With the increasing incidence of community-acquired-methicillin-resistant *S. aureus* (CA-MRSA), vancomycin has become the primary choice for therapy when that organism is suspected. Vancomycin or clindamycin are used when 10% or more of community *S. aureus* isolates are known to be methicillin resistant (Liu et al, 2011). However, presence of inducible resistance to clindamycin limits its use and vancomycin requires careful dose adjustments to maintain appropriate concentrations in the blood. Clearly, the seriousness of the condition, with its potential for limb-threatening outcomes, strongly suggests a need for the development of additional antimicrobial agents.

Dalbavancin is a lipoglycopeptide which is highly active against Gram-positive bacteria, including *streptococci*, *S. pneumoniae* and *S. aureus*, including MRSA; the MIC₉₀ for *S. aureus* is 0.06 µg/mL. In addition, dalbavancin has a half-life of approximately 14 days, allowing for once weekly dosing. In adults, dalbavancin (given as 1000 mg on Day 1 followed by 500 mg on Day 8), has been shown to be non-inferior both to linezolid alone and to a comparator regimen including vancomycin and linezolid in the treatment of acute bacterial skin and skin structure infections (ABSSSI)/complicated skin and skin structure infections (cSSSI) in multiple randomized, double-blinded studies (VER001-9, DUR001-301 and DUR001-302). Dalbavancin was well tolerated in these studies, with a higher proportion of patients in the comparator group reporting an adverse event (AE) as compared with dalbavancin. The most common AEs reported with dalbavancin were gastrointestinal complaints (nausea, diarrhea) and headache.

Pharmacokinetics in Bone and Related Tissue

The pharmacokinetics of dalbavancin in bone and synovial tissue have been studied in a Phase 1 study in adults undergoing elective orthopedic surgery (DUR001-105). Adults scheduled for elective orthopedic surgery were assigned to one of 6 cohorts, for tissue sampling at 12 hours, 24 hours, 72 hours, 168 hours, 240 hours or 336 hours post dose. Enrolled subjects received a single 1000 mg dose of dalbavancin at the appropriate time point prior to scheduled surgery. Thirty-one subjects received dalbavancin in order to obtain 30 evaluable bone samples. The mean concentration of dalbavancin in bone at 12 hours post dose was 6.3 ± 3.2 µg/g, and remained > 10-fold above the MIC₉₀ of *S. aureus* through the final sample collection at 336 hours (14 days) (see Table below). The mean bone:plasma AUC penetration ratio was 13.9%. The concentration of dalbavancin in synovial fluid at 12 hours post dose was 22.9 µg/mL and also remained above MIC₉₀ of *S. aureus* through final sample collection. Similar values were seen in synovial tissue.

Table: Dalbavancin tissue concentrations in DUR001-105 (Dunne et al)

Tissue	Dalbavancin concn (mean [SD]; no. of samples) at hours (days) postdose that samples were collected:					
	12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (µg/ml) ^a	85.3 (18.9); 31	ND ^b	ND	ND	ND	15.3 (4.1); 31
Synovium (µg/g) ^c	25.0 (0); 3	17.9 (7.8); 3	19.5 (4.9); 3	19.2 (8.9); 4	25.0 (0); 2	15.9 (7.9); 3
Synovial fluid (µg/ml) ^c	22.9; 1	27.4 (10.8); 4	19.2 (4.9); 3	11.6 (3.3); 2	13.9 (1.0); 3	6.2 (1.7); 2
Bone (µg/g)	6.3 (3.1); 5	5.0 (3.5); 5	4.6 (3.8); 5	3.8 (2.7); 5	3.7 (2.2); 5	4.1 (1.6); 5
Skin (µg/g) ^c	19.4 (7.9); 2	12.5 (6.5); 3	13.8 (1.4); 2	15.7 (1.0); 2	21.6; 1	13.8 (2.1); 2

^a Mean (SD) plasma concentrations in 31 subjects at 772 and 1,080 h were 6.2 (2.4) and 3.4 (1.7), respectively.

^b ND, not detected.

^c Concentrations above the upper limit of quantification are reported as 25 µg/unit.

Animal model of osteomyelitis

Dalbavancin was studied in a rat model of *S. aureus* sternal osteomyelitis. Rats with *S. aureus* sternal osteomyelitis were treated with one of 3 regimens: dalbavancin (20 mg/kg loading dose followed by 10 mg/kg daily), vancomycin (given IP, 50 mg/kg, q12h) or saline treatment for 7 days and 14 days; efficacy in reducing sternal bone bacterial counts was assessed. Dalbavancin showed superiority compared to saline at 7 days (0.75 log reduction in bone CFU) and at 14 days treatment (> 3-log reduction in bone CFU). Treatment with 7 days of dalbavancin reduced systemic dissemination of MRSA compared to saline (5% vs 33%). Results were similar to those achieved by vancomycin therapy. This study demonstrated the effectiveness of dalbavancin using doses mimicking human PK in the treatment of MRSA rat sternal osteomyelitis and confirms that dalbavancin in bone is available for the killing of bacterial pathogens.

The prolonged half-life of dalbavancin, which allows for once weekly dosing, maintains serum concentrations above the MIC₉₀ for most Gram-positive pathogens, including *S. aureus*. The demonstrated distribution of dalbavancin into bone and related tissues is also reassuring. The 2-dose, once weekly dosing regimen offers advantages to patients and physicians regarding the need for prolonged intravenous access and compliance with an anti-infective treatment course for a disease with a treatment duration of 4-6 weeks.

More complete information about dalbavancin is found in the current Investigator's Brochure.

8.0 **STUDY OBJECTIVES**

Primary-

- To determine the efficacy of dalbavancin for the treatment of the first episode of osteomyelitis known or suspected to be caused by Gram-positive pathogens in adults

Secondary-

- To assess the safety and tolerability of dalbavancin in adult patients with osteomyelitis
- To estimate the clinical response rate per pathogen in the dalbavancin group at the end of therapy (Day 42) and Day 180
- To estimate the clinical response rate in the dalbavancin group at Day 21, Day 180 and Day 365
- 

9.0 **INVESTIGATIONAL PLAN**

9.1 **OVERALL STUDY DESIGN AND PLAN: DESCRIPTION**

This clinical study will be a single-center, randomized, open-label, active-controlled, parallel-group study comparing dalbavancin to standard of care (SOC) therapy in osteomyelitis. Patients randomized to the dalbavancin treatment group will receive 2 doses of dalbavancin 1 week apart and patients in the SOC treatment group will receive SOC therapy for 4 to 6 weeks of treatment with SOC therapy. Patients will then be followed up for a period of 365 days.

The Schedule of Assessments and Procedures is presented in [Section 2.0](#). Detailed descriptions of each study visit can be found in [Section 9.5.1](#).

9.2 **DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS**

An open-label, randomized, parallel-arm study design was chosen because of the challenges with conducting a blinded study with various treatment options and dosing schedules.

There will be 2 open-label treatment groups: dalbavancin 1500 mg IV on Day 1 and Day 8, and oral or IV SOC antibiotic for osteomyelitis based on investigator judgment for 4-6 weeks. The 2 groups will be randomized in a 7:1 ratio (70 patients in the dalbavancin treatment group and 10 patients in the SOC treatment group).

The SOC treatment group will serve as a contemporaneous illustration of typical SOC regimens used at the study site, and to help assess generalizability of study findings, since the study will be done in a single site in the Ukraine. A small comparator group (n = 10) is preferred over extrapolating from historical controls that may be very different from study cohort, and would likely lack efficacy data and inflammatory markers at the same time points as the dalbavancin treatment group.

9.3 **SELECTION OF STUDY POPULATION**

9.3.1 **Inclusion Criteria**

To be eligible to participate in the study, a patient must meet the following criteria:

1. Male or female, ≥ 18 years old

2. A diagnosis of osteomyelitis (first episode) defined by:
 - Pain or point tenderness upon palpation or probing to bone
 - Plain radiograph or MRI consistent with osteomyelitis (indistinctly marginated edema-like pattern of bone marrow hypointensity on unenhanced T1-weighted sequences, hyperintensity on fat-saturated T2-weighted and STIR sequences and/or abnormal enhancement on gadolinium-enhanced fat-saturated T2-weighted sequences, with or without visible periostitis or cortical bone destruction)

OR

Gram-positive cocci documented on a baseline Gram-stain from a bone specimen

 - Elevated CRP (low sensitivity) above the upper limit of normal (ULN) (reference range for low sensitivity CRP is 3-10 mg/L)
3. A signed and dated written informed consent document indicating that the subject (or a legally authorized representative) has been informed of all pertinent aspects of the study.
4. Subjects must be willing and able, if discharged from the hospital, to return to the hospital or a designated clinic for scheduled visits, treatment, laboratory tests, and other outpatient procedures as required by the protocol.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Treatment with an investigational drug within 30 days preceding the first dose of investigational product.
2. Receipt of > 24 hours of potentially effective IV antibacterial therapy for osteomyelitis within 96 hours of randomization, unless the pathogen isolated was documented to be MRSA that was resistant to the administered antibiotic.
3. A prior episode of osteomyelitis, or a failed course of therapy for osteomyelitis.
4. Infection associated with a burn wound, with a sacral decubitus ulcer, or with multiple sites of osteomyelitis.

5. Septic arthritis that is non-contiguous to osteomyelitis, as diagnosed by isolation of a pathogen from synovial fluid culture.
6. Immunosuppression/immune deficiency, including hematologic malignancy, recent bone marrow transplant (in post-transplant hospital stay), absolute neutrophil count < 500 cells/mm³, receiving immunosuppressant drugs after organ transplantation, receiving oral steroids for an extended period of time (> 20 mg prednisolone per day or equivalent), chronic granulomatous disease, and known or suspected human immunodeficiency virus (HIV) infection with a CD4 cell count < 200 cells/mm³ or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition and unknown CD4 count.
7. Evidence of Gram-negative bacteria by Gram stain in the absence of Gram-positive organisms.
8. Gram-negative bacteremia, even in the presence of Gram-positive infection or Gram-positive bacteremia. Note: If a Gram-negative bacteremia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative bacteremia.
9. Evidence of fungus or mycobacteria at baseline
10. Patients with concomitant endocarditis, necrotizing fasciitis, or prosthetic material at the site of infection at the time of study initiation.
11. Patients with an infection involving a limb with evidence of critical ischemia defined as any of the following criteria: absent or abnormal Doppler wave forms, toe blood pressure of < 45 mm Hg, ankle brachial index < 0.5 , and/or critical ischemia as assessed by a vascular surgeon.
12. Infection due to an organism known prior to study entry to not be susceptible to dalbavancin (dalbavancin mean inhibitory concentration [MIC] > 0.12 μ g/mL) or vancomycin (vancomycin MIC > 2 μ g/mL).
13. Concomitant systemic antibacterial therapy for Gram-positive infections (eg, rifampin, gentamicin).
14. Concomitant condition requiring any antibiotic therapy that would interfere with the assessment of study drug for the condition under study.
15. Known or suspected hypersensitivity to glycopeptide antibiotics.
16. Patients with a rapidly fatal illness, who are not expected to survive for 3 months.

17. Pregnant or nursing females; positive urine (or serum) pregnancy test at Screening (pre-menopausal females only) or after admission (prior to dosing)
18. Sexually active females of childbearing potential who are unwilling or unable to use an acceptable method of contraception from at least the first dose of study drug until the last pregnancy test.
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.
20. Unwilling or unable to follow study procedures.
21. Employee or immediate relative of an employee of Durata Therapeutics, Inc., any of its affiliates or partners, or the study site.

9.3.3 Removal of Patients From Therapy or Study Assessment

Patients should be encouraged to complete all study assessments. However, a patient may be discontinued from study drug therapy or may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the patient is otherwise entitled.

A premature discontinuation from the study will occur when a patient who signed the ICF, regardless of circumstances, ceases participation in the study, before the completion of all study assessments (ie, before completing all protocol-stipulated activities).

Follow-up of patients prematurely discontinued from study drug or withdrawn from the study will be conducted as described below.

9.3.3.1 Premature Discontinuation From Study Drug

Reasons: Possible reasons for premature discontinuation from study drug administration include, but are not limited to:

- Occurrence of an AE that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from IV study drug
- Known pregnancy or breastfeeding during the study therapy administration period. A female patient whose pregnancy test is positive at Day 28 or 42 must be followed through the immediate postnatal period or until termination of the pregnancy. Study center personnel must report every pregnancy as soon as possible (within 24 hours of learning of the pregnancy; as described in [Section 9.5.2.7](#)).

- The patient meets criteria for drug-induced liver injury per [Appendix III](#), at the discretion of the Investigator
- Patient has an insufficient therapeutic response to study drug. A patient who does not show signs of improvement despite treatment with study drug for an appropriate length of time or a patient who shows signs of clinical worsening at any time may be prematurely discontinued from study therapy.
- If a Gram-negative bacteremia or fungemia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative bacteremia.
- Patients from whom only a Gram-negative pathogen is isolated from blood and/or bone culture should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative infection.
- Investigator determines that it is in the best interest of the patient to discontinue study drug, due to reasons other than an AE

Assessments and Procedures: A patient who is prematurely discontinued from study drug should have the assessments for premature discontinuation conducted at the time of discontinuation as outlined in [Table 2-1](#). A clear description of reason for premature discontinuation from study drug must be documented. If a patient is discontinued from study drug due to insufficient therapeutic effect and is switched to an alternative antibiotic, that therapy should be recorded. The reasons for premature discontinuation from study drug will be reflected on the relevant disposition page of the eCRF. Patients who discontinue from study therapy should continue to have follow-up safety visits.

9.3.3.2 *Withdrawal From Study*

Reasons: Possible reasons for withdrawal from study depend on the timing of the withdrawal, and include, but are not limited to:

- Screen failure (failure to meet inclusion/exclusion criteria) (before administration of first dose of study therapy)
- Withdrawal of consent (a clear reason must be documented)
- AE (before administration of first dose of study therapy)
- Protocol deviation/violation, including lack of compliance

- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- Study or site prematurely terminated by Sponsor for any reason

An AE should not be a reason for withdrawal from study after study drug has been administered. The patient may be discontinued from study drug due to an AE, in which case they should be encouraged to stay in the study for follow-up safety assessments.

Note: If death was due to an AE, then the AE is the reason for discontinuing study drug and death is the reason for withdrawal from study. If the death is due to lack of efficacy, then lack of efficacy is the reason for discontinuing study drug, and death is the reason for withdrawal from study.

Assessments and Procedures: Patients may withdraw from the study, or be withdrawn at the request of the Investigator or Sponsor. A patient who is withdrawn from the study should be encouraged to undergo the assessments for premature discontinuation conducted as outlined in [Table 2-1](#) on the day of withdrawal. Patients who do not complete all scheduled visits/procedures must be requested in writing to come in for a premature discontinuation visit and to return any unused investigational product. A copy of the letter, together with the source documentation, will be kept by the Investigator. A clear description of reason for withdrawal from study must be documented. The reasons for withdrawal from the study will be reflected on the relevant disposition page of the eCRF.

9.3.4 Patient Replacement Procedures

Randomized patients who are withdrawn will not be replaced.

9.4 TREATMENTS

9.4.1 Treatments Administered

9.4.1.1 *Dalbavancin Treatment Group*

Patients randomized to the dalbavancin treatment group will receive treatment as follows:

- Normal renal function (and patients receiving regular hemodialysis or peritoneal dialysis): dalbavancin 1500 mg IV over 30 (\pm 5) minutes on Day 1 and Day 8.
- Chronic renal insufficiency (with a serum creatinine clearance of $<$ 30 mL/min and not receiving regular hemodialysis): dalbavancin 1000 mg IV over 30 (\pm 5) minutes on Day 1 and Day 8

9.4.1.2 *Standard of Care Treatment Group*

Patients randomized to the SOC comparator treatment group will receive an antibiotic consistent with SOC for osteomyelitis based on Investigator judgment. The duration of treatment will be 4-6 weeks.

9.4.1.3 *Other Additional Antibacterial Therapy*

Aztreonam may be administered at randomization for presumed co-infection with a Gram-negative pathogen and could be discontinued if a Gram-negative pathogen is not documented by culture results. A switch to an oral antibiotic for coverage of Gram-negative pathogens is allowed once evidence of clinical improvement has been established.

Metronidazole (IV or oral) or oral vancomycin may be used for *Clostridium difficile* infections.

Other antibiotics that do not achieve significant therapeutic concentrations in the serum (eg, nitrofurantoin) may be considered for the treatment of other concomitant infections. Close consultation with the medical monitor is advised prior to use of these antibiotics.

9.4.1.4 *Duration of Treatment*

The total duration of study therapy will be 2 doses of dalbavancin given 1 week apart, and 4 to 6 weeks of comparator treatment.

9.4.2 Identity of Investigational Products

Dalbavancin for Injection is supplied as a single-use vial of sterile, lyophilized preservative-free powder containing dalbavancin hydrochloride equivalent to 500 mg of dalbavancin. Each vial should be reconstituted and further diluted prior to administration by addition of 5% dextrose (5% glucose) solution (D5W) in accordance with the study pharmacy manual. The study center is responsible for providing the appropriate commercially available diluents required for preparation and administration of IV infusion.

Investigational dalbavancin will be labeled based on local regulations. Immediately before dispensing investigational dalbavancin, the Investigator will write the patient identification number, patient's initials, and date on the label.

With the exception of dalbavancin, all other study drugs (oral or parenteral) will be commercially labeled and supplied by the study site. If aztreonam is not available locally, it will also be labeled and supplied by the Sponsor. All study drugs should be kept in a secure place under appropriate storage conditions, as specified on the drug labeling and package insert.

The Investigator or designee is responsible for recording the receipt and use of all investigational products supplied and for ensuring the supervision of the storage and allocation of these supplies. Upon completion of the study or termination of the site, all unused study drugs that were not dispensed will be shipped to a site designated by the Sponsor.

Refer to the Pharmacy Manual for additional information.

9.4.3 Method of Assigning Patients to Treatment Groups

Patients will be randomly assigned 7:1 to the dalbavancin or SOC treatment group.

At the time of signing the ICF and consenting to participate in this study, each patient will be assigned a unique 8-digit patient identification number consisting of a 3-digit study center number followed by a 2-digit protocol number and then a 3-digit unique patient number for the study center. The first patient to sign the ICF at the study center will be assigned the first number in the sequence by the study center, and each subsequent patient will be assigned the next sequential number. This patient identification number will be used to identify the patient at all phases of the study.

A list of patient randomization numbers will be generated by Statistical Programming at Actavis. The study center will be provided with the list of randomization numbers and the corresponding treatment group assignment (dalbavancin or SOC comparator). Randomization numbers will be assigned consecutively (eg, 1, 2, 3,...) by the Investigator (or appropriately trained designee) at the time the patient is randomized into the treatment group (ie, the first patient randomized will be assigned to the first number in the sequence and assigned to the associated treatment group). The treatment group assignment will be blinded until the time of randomization.

Refer to the Pharmacy Manual for additional information.

9.4.4 Selection of Dosages in the Study

A 2-dose regimen of 1500 mg of dalbavancin administered 1 week apart is proposed for treatment of osteomyelitis in adults for the following reasons:

- The safety of a single 1500 mg dose has been previously evaluated in approximately 60 healthy adult volunteers. The single 1500 mg dose was also administered (over 30 minutes) to over 300 patients with ABSSSI in the recently completed Phase 3 trial DUR001-303, with comparable safety and efficacy to the two-dose regimen (1000 mg on Day 1, followed by 500 mg on Day 8). While a 25 mg/kg dose was also studied in a small number of children and was also well tolerated, it was only studied in children < 6 years of age.
- A total dose of 4500 mg over 8 weeks was safely administered and well-tolerated in a phase 1 study of extended duration dosing (DUR001-104), with no apparent accumulation (1000 mg of dalbavancin on Day 1 followed by 500 mg weekly for 7 additional weeks) (Dunne, 2015).
- The 2-dose regimen of 1500 mg of dalbavancin administered 1 week apart was derived from data from the bone penetration study (DUR001-105) and extended duration dosing study (DUR001-104), along with population PK modeling (Dunne, 2015).
- The pharmacokinetic/pharmacodynamic parameter that correlated best with dalbavancin's efficacy is AUC/MIC. The 2-dose regimen of 1500 mg administered 1 week apart is expected to achieve an AUC similar to that for a 1000 mg initial dose, followed by 4 subsequent 500 mg weekly doses (Dunne, 2015).

- In animal models ([Andes, 2007](#)), delivery of the same total dose of dalbavancin earlier in the course of therapy was associated with a better likelihood of success relative to the same total dose given in smaller amounts over longer periods of time. Assuming these findings in animals pertain to human infection, 2 doses of dalbavancin within the first 8 days may be more likely to be effective relative to the same total dose over approximately 6 weeks.
- The proposed dose will also provide dalbavancin exposures in plasma which exceed the MIC₉₀ for *S. aureus* for greater than 42 days (6 weeks).
- Delivery of only 2 doses of dalbavancin avoids the need for a central catheter and the need for delivery of intravenous medications at home.

The dosing regimen for the SOC comparators will be based on the relevant prescribing information for those medications and standard clinical care for patients with osteomyelitis. The total treatment duration for patients in the SOC treatment group is expected to be 4-6 weeks.

9.4.4.1 Dose Adjustments - Dalbavancin

In the case of renal impairment, at any time, the dose of dalbavancin (including the initial dose) may be adjusted by the pharmacist or designee per the dosage regimen in [Table 9.4.4.1-1](#). At any time, the dose of dalbavancin may be readjusted to the appropriate dosage when renal function improves.

Table 9.4.4.1–1. Dalbavancin Dosage Adjustments for Renal Impairment

<i>Estimated Creatinine Clearance (mL/min)^a</i>	<i>Recommended Dosage Regimen</i>
≥ 30 and patients receiving regular hemodialysis or peritoneal dialysis	No adjustment: 1500 mg IV (over 30 minutes) on Day 1 and Day 8
< 30	1000 mg IV (over 30 minutes) on Day 1 and Day 8

a As calculated using the Cockcroft-Gault formula.
 IV = intravenously.

Estimate CrCl using the following Cockcroft-Gault formula, based on serum creatinine concentrations obtained at Baseline and Day 8, and using ideal body weight instead of actual weight.

$$\text{Males: CrCl} = \frac{(140 - \text{age in years}) \times \text{Ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: CrCl} = \frac{(140 - \text{age in years}) \times \text{Ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

Ideal body weight is calculated as:

Males:

If height (H) > 152.5 cm
 Ideal body weight = 50 + [(H – 152.4) x 0.89]
 If H < 152.5 cm
 Ideal body weight = 50 – [(152.4 – H) x 0.89]

Females:

If H > 152.5 cm
 Ideal body weight = 45.4 + [(H – 152.4) x 0.89]
 If H < 152.5 cm
 Ideal body weight = 45.4 – [(152.4 – H) x 0.89]

9.4.4.2 Dose Adjustments - Other Investigational Products

For all other investigational products, appropriate dosage modifications for renal function will be made per the respective package insert or institutional guidelines.

9.4.5 Blinding

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

9.4.6 Unblinding

Not applicable

9.4.7 Prior and Concomitant Therapy

Receipt of more than 24 hours of potentially effective intravenous antibacterial therapy for osteomyelitis within 96 hours of randomization is not allowed (unless the pathogen isolated was documented to be MRSA that was resistant to the administered antibiotic). Treatment with an investigational drug within 30 days prior to the first dose of study medication is not allowed. A patient who has had a prior failed course of therapy for osteomyelitis should not be enrolled.

Drugs Not Allowed as Concomitant Medications (up to Day 42)-

- Systemic antibacterial therapy for Gram-positive infections (eg, rifampin, gentamicin).
- Concomitant antibiotic therapy that would interfere with the assessment of study drug

Drugs Allowed as Concomitant Medications-

- Aztreonam may be administered at randomization for presumed co-infection with a Gram-negative pathogen and could be discontinued if a Gram-negative pathogen is not documented by culture results. A switch to an oral antibiotic for coverage of Gram-negative pathogens is allowed once evidence of clinical improvement has been established.
- Metronidazole (IV or oral) or oral vancomycin may be used for *Clostridium difficile* infections.
- Other antibiotics that do not achieve significant therapeutic concentrations in the serum (eg, nitrofurantoin) may be considered for treatment of other concomitant infections. Close consultation with the medical monitor is advised prior to use of these antibiotics.

Surgical debridement should be performed on any patient if clinically indicated.

9.4.8 Monitoring Treatment Compliance

Treatment compliance will be closely monitored by recording the date, time, and whether or not each dose of IV study drug was completely infused and, if applicable, whether or not each intended dose of oral therapy was taken.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy Assessments

9.5.1.1 *Primary and Secondary Efficacy Assessments*

9.5.1.1.1 *Primary Efficacy Assessment*

Clinical response at Day 42 in the Clinically Evaluable (CE) population.

Clinical response can be either cure, failure, or indeterminate:

- Cure is defined as recovery without need for additional antibiotic therapy.
- Failure is defined as:
 - Requirement of additional antibiotic therapy for no response or worsening after improvement
 - New purulence
 - Amputation due to progression of infection (from initiation of study drug to outcome assessment visit).
 - Requiring > 6 weeks of antibiotic therapy for patients in the comparator arm
 - Death (for any reason).
- Indeterminate is defined as:
 - Lost to follow-up
 - Amputation due to vascular insufficiency (from initiation of study drug to outcome assessment visit).

9.5.1.1.2 *Secondary Efficacy Assessments*

- Clinical improvement at Day 21 in the modified ITT (mITT) and CE populations
 - Clinical improvement at Day 21 is defined as no worsening of pain from baseline (if present at baseline) (subjective pain and/or point tenderness) and improvement in inflammation (as measured by C-reactive protein).
- Clinical response (cure, failure, or indeterminate) at Day 42 in the mITT and micro-mITT populations

- Clinical response (cure, failure, or indeterminate) at Day 180 in the mITT and CE Populations
- Clinical response (cure, failure, or indeterminate) at Day 365 in the mITT and CE Populations
- Clinical response (cure, failure, or indeterminate) by pathogen at Day 42 and Day 180 in the CE Population

9.5.1.2 *Microbiological Assessments*

9.5.1.2.1 *Blood Samples for Culture*

Peripheral blood culture must be drawn at Baseline (prior to study drug treatment), not through an existing intravascular line. If blood cultures are positive at Baseline, they should be repeated once every 24 hours until negative. At the Day 8 visit, results of all prior blood cultures should be checked and blood cultures should be repeated if previous blood cultures were positive. If clinically indicated, blood cultures should be collected at the time of treatment discontinuation or for determination of treatment failure.

Blood cultures should be repeated upon knowledge of a positive result from any visit until clearance of bacteremia is confirmed.

When blood cultures are required, 2 sets of blood samples (1 aerobic and 1 anaerobic bottle) should be obtained from 2 separate venipuncture sites.

Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility to all study drugs used at the study site.

Microbiological specimens and isolates will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

9.5.2 *Safety Assessments*

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit, and the evaluation must be documented.

9.5.2.1 *Adverse Events*

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, unless the event is captured in the study endpoint, as defined below; the event need not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A). For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE) requiring immediate notification to the Sponsor. All AEs will be followed up by the investigator until the event or its sequel resolve or stabilize at a level acceptable to the investigator, and the Sponsor concurs with that assessment.

For the purpose of the site's data collection responsibilities, all AEs should be recorded on the CRF from the time the patient signed the ICF until the final protocol-defined study visit.

An event would be considered as adequately captured in the study endpoint if it is accurately and fully represented by a protocol-defined reason for clinical failure (other than mortality) or relapse. Such an event should not be reported as an adverse event unless it is a serious adverse event as defined in this protocol ([Section 9.5.2.4](#)). Events represented by the study endpoints include all of the following:

- Increase or no change in pain and/or point tenderness (compared with baseline)
- Increase or no change in CRP (compared with highest value)
- Requirement of additional antibiotic therapy for no response or worsening after improvement
- New purulence
- Amputation due to progression of infection (from initiation of study drug to outcome timepoint).
- Requiring > 6 weeks of antibiotic therapy for patients in the comparator arm
- Lost to follow-up
- Amputation due to vascular insufficiency (from initiation of study drug to outcome timepoint)

Except for circumstances as defined above, examples of AEs include but are not limited to:

- Abnormal test findings (see Section 9.5.2.1.1)
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation of study drug;
- Exposure during Pregnancy

Please note medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

Pregnancies should not be automatically assessed as AEs ([Section 9.5.2.7](#)).

9.5.2.1.1 Abnormal Test Findings

An abnormal objective test finding (e.g., an abnormal liver function test result) should be reported as an AE if the following conditions apply:

- Test result is associated with accompanying symptoms and/or signs, constituting a clinical syndrome (e.g., abnormal liver function test results, jaundice, and hepatic tenderness suggesting a diagnosis of hepatitis), and/or

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or withdrawal from the study, significant additional concomitant drug treatment, or other therapy.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not define the abnormal objective test finding as an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE. Additional diagnostic testing or medical/surgical interventions that occur as a result of an adverse event due to an abnormal lab test finding should be noted in the CRF.

9.5.2.2 Causality Assessment

For each AE (serious and non-serious), the Investigator must provide an assessment of causal relationship to the investigational product. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. If the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records. Specifically, the investigator will choose whether the AE is unrelated, unlikely related, possibly related or probably related to the investigational product.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

The Investigator will assess causality of the event in relation to dalbavancin based on the following defined criteria:

- **UNRELATED:** No relationship between the event and medicinal product
- **UNLIKELY:** Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); disease or other drugs provide plausible explanations

- **POSSIBLY:** Event or laboratory test abnormality, with reasonable time relationship to drug intake; could also be explained by disease or other drugs; information on drug withdrawal may be lacking or unclear
- **PROBABLY:** Event or laboratory test abnormality, with reasonable time relationship to drug intake; unlikely to be attributed to disease or other drugs; response to withdrawal clinically reasonable; rechallenge not required

9.5.2.3 *Severity Assessment*

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4). Severity will be assessed according to the following scale:

- Mild:** Does not interfere with the patient's usual function.
- Moderate:** Interferes to some extent with the patient's usual function.
- Severe:** Interferes significantly with the patient's usual function.

9.5.2.4 *Serious Adverse Events*

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of investigational product dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

For SAEs, the reporting period to the Sponsor begins from the time that the patient provides informed consent, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through the Final Visit. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

9.5.2.4.1 *Hospitalization*

Adverse events associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., patient has no place to sleep);

- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery). Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as an AE. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

9.5.2.5 *Reporting Adverse Events and Serious Adverse Events*

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, “How do you feel since your last visit?” Study site personnel will record all pertinent information in the patient’s eCRF.

All AEs must be recorded on the appropriate AE reporting page of the patient’s eCRF whether or not they are considered causally related to the investigational product.

For every AE, the Investigator must:

- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and causal relationship
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

In addition, patients are to be reminded, as described in the ICF and in accordance with [Section 9.5.2.1](#), to notify site personnel of any AEs occurring from the time the patient signed the ICF until the final protocol defined study visit.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the investigational product. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

For SAEs, the reporting period to the Sponsor begins from the time that the patient provides informed consent, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through the Final Visit. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

9.5.2.6 *Immediate Reporting of Serious Adverse Events and Events of Special Interest*

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study site personnel must report the event to Actavis Global Drug Safety on the SAE Form for Clinical Trials. The Sponsor's Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The site must transmit the SAE Form for Clinical Trials to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed within 24 hours of knowledge of the event at the study site.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. ***The Sponsor may contact the study site to solicit additional information or follow up on the event.***

Fax the SAE Form for Clinical Trials to Actavis, Inc.

[REDACTED]

[REDACTED]

9.5.2.7 *Reporting of Pregnancies Occurring During the Study*

An exposure during pregnancy occurs if a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure). Within 24 hours of learning of the pregnancy, the study site personnel must report the event to Actavis Global Drug Safety on the Clinical Trial Pregnancy Form and fax it to the SAE/Pregnancy fax number stated in [Section 9.5.2.6](#), even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up a Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in Section 9.5.2.6 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Form.

9.5.2.8 *Potential Hy's Law Cases*

Criteria for potential Hy's Law cases are as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ ULN
AND
- Total bilirubin $\geq 2 \times$ ULN AND
- Alkaline phosphatase (ALP) $< 2 \times$ ULN

Study site personnel must report every patient who meets these criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24 hour period. This requirement applies from the time the patient signs the ICF for the study until the final protocol-defined study visit.

The Investigator must notify the Sponsor immediately when the above criteria have been met. A potential Hy's law case must be faxed to the Sponsor on an AE of Special Interest Form as soon as possible (within 24 hours of learning of the potential Hy's law) to the SAE/Pregnancy fax number stated in [Section 9.5.2.6](#), even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Physician and in accordance with FDA guidance ([US Food and Drug Administration, 2009](#)).

9.5.2.9 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected according to the Schedule of Assessments and Procedures ([Table 2-1](#)).

Women of childbearing potential (including those who are fewer than 2 years postmenopausal) will be required to have a serum pregnancy test at baseline. The test must be negative before randomization. If the serum test results cannot be obtained before randomization, a urine pregnancy test may be used for enrollment.

The following clinical laboratory levels will be measured:

Hematology: Basophils (absolute count and %), eosinophils (absolute count and %), erythrocyte count, hematocrit, hemoglobin, lymphocytes (absolute count and %), monocytes (absolute count and %), neutrophils (absolute count and %), immature neutrophils (bands; %), platelet count

Chemistry: Albumin, ALP, AST, ALT, bilirubin (total and direct), blood urea nitrogen, calcium, creatinine, electrolytes (ie, bicarbonate, chloride, potassium, sodium), gamma-glutamyl transferase, glucose (nonfasting), lactate dehydrogenase, magnesium, protein (total)

Other: CRP, ESR, pregnancy test

The site's local laboratory will be used to evaluate all laboratory samples.

Results from unscheduled laboratory tests will not be collected, unless associated with an SAE or AE leading to discontinuation of IV study drug.

Any abnormal laboratory test possibly attributable to IV study drugs, or of clinical significance, will be repeated at appropriate intervals until stabilization; results from these unscheduled laboratory tests should be collected.

9.5.2.9.1 Potential Drug-Induced Liver Injury/Hy's Law

See [Section 9.5.2.8](#).

9.5.2.10 Vital Signs, Body Weight, and Height

Vital signs will be recorded at every visit; the parameters are:

- Blood pressure: systolic and diastolic - to be taken after the patient has been sitting for 5 minutes
- Pulse rate: to be taken after the patient has been sitting for 5 minutes
- Respiratory rate
- Temperature (oral, rectal, or tympanic): if taken multiple times, record the highest daily temperature

Body weight and height will be measured at baseline. If height or weight is not obtainable (eg, patient is immobilized), the last known or stated height and weight may be used.

9.5.2.11 Physical Examination

A complete physical examination (including targeted examination of the infection site) will be conducted at Baseline by a professionally trained physician or health professional licensed to perform physical examinations.

A targeted examination of the infection site will be performed at Day 8, 21, 28, 42, 180, and 365 as well as upon premature discontinuation.

The same medically trained individual should perform all assessments, if possible. Patients may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessments.

[REDACTED]

| [REDACTED]

| [REDACTED]

[REDACTED]

| [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

| [REDACTED]

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Recording and Documentation

Data collection will involve the use of the Actavis electronic data capture (EDC) system, to which only authorized personnel will have access. Patient's data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edit checks, data monitoring and reviews, queries may be electronically issued to the site and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date, and time) to assist the Sponsor and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator prior to final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents, etc) will be retained at the site, along with adequate source documentation, according to regulatory requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and regulatory or other health authorities.

9.6.2 Data Monitoring

Before any patient enters the study, a representative of the Sponsor will meet with the Investigator and the study site staff to review the procedures to be followed during the study. EDC functionality training is provided via computer-based training to train investigators and authorized designees on recording the data in the eCRFs using the EDC system. After the first patient is enrolled, the Sponsor representative, a Regional Site Manager (RSM) or designee, will periodically monitor the progress of the study by conducting on-site visits. This RSM or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the Investigator and the study site staff. The Investigator will make available to the RSM or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study site staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Analysis Populations

Analysis Populations are described below.

9.7.1.1 *Screened Population*

The Screened Population will consist of all patients who undergo the Baseline Visit and receive a patient identification number.

9.7.1.2 *Intent-to-Treat Population*

The Intent-to-Treat Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

9.7.1.3 *Safety Population*

The Safety Population will be a subset of the ITT Population and will include all randomized patients who receive any amount of randomized medication. Patients will be analyzed according to the treatment actually received.

9.7.1.4 Modified Intent-to-Treat Population

The mITT Population will be a subset of the ITT Population and will include all randomized patients who receive any amount of randomized medication and meet the criteria for known or suspected Gram-positive osteomyelitis ([Inclusion Criterion 2](#)). Patients from whom only a Gram-negative pathogen is isolated from blood and/or bone culture will be excluded from the mITT. Patients whose cultures include both a Gram-positive and a Gram-negative pathogen will remain in the mITT. Patients will be analyzed according to randomized treatment group, regardless of treatment received.

9.7.1.5 Clinically Evaluable Population

The CE Population will be a subset of the mITT Population and will include patients who meet both of the following specific conditions for evaluability:

- For patients randomized to receive dalbavancin, received at least 1 dose of active study medication. For patients randomized to comparator, received at least 2 weeks of study medication
- Received no more than 1 dose of another (non-study) systemic antibacterial therapy with documented activity against the causative organism, from study drug initiation until the outcome assessment visit, for an indication other than osteomyelitis. [Note: patients receiving a non-study systemic antibacterial treatment for the treatment of osteomyelitis from initiation of study drug through the outcome assessment visit will be assessed as EVALUABLE FAILURES]

9.7.1.6 Microbiological mITT Population

The microbiological mITT (micro-mITT) population will be a subset of the mITT population and will include patients with a Gram-positive pathogen isolated from blood and/or bone specimen. Patients whose cultures include both a Gram-positive and a Gram-negative pathogen will remain in the micro-mITT.

9.7.2 Patient Disposition

Patient disposition (enrollment, discontinuations from study drug and the study) by treatment group will be provided based on the ITT Population. Reasons for exclusion from study populations will be summarized for the ITT Population.

The number of patients in the Safety and ITT Populations will be summarized by treatment group; the Screened Analysis Set will only be summarized overall.

Screen failures (ie, patients screened but not randomized) and the associated reasons for failure will be tabulated overall.

The number and percentage of patients who complete the treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT Population. The reasons for premature discontinuation from the treatment period as recorded on the termination pages of the eCRF will be summarized (number and percentage) by treatment group for all randomized patients.

9.7.3 Demographics and Other Baseline Characteristics

Demographics (eg, age, race, gender, body mass index), medical and surgical history, description of the infection by pathogen, markers of disease severity and co-morbidities (eg, presence of bacteremia, renal impairment), baseline assessment of the clinical signs and symptoms, and microbiological assessment of the infection site will be summarized by treatment group in the mITT Population.

Prior medication is defined as any medication taken before the date of the first dose of investigational product. Concomitant medication is defined as any medication started on or after the date of the first dose of investigational product. Any prior medications stopped more than 3 days before the date of the first dose of investigational product and any concomitant medications started after the date of the last dose of investigational product will not be presented in the summary tables, but will be included in the patient data listings. Medications that are ongoing at the time of first dose of randomized medication will be counted both as prior and concomitant.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple administrations of the same medication to a patient will be counted only once for the given patient. Medication-related summaries will be presented separately by “systemic antimicrobial medications” and “other medications not in this class” subgroups.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to study drug will be summarized by treatment group for the Safety Population. Calendar days of exposure will be calculated as the number of calendar days on study drug. For each type of exposure descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) will be presented.

9.7.4.2 Measurement of Treatment Compliance

Each patient's compliance with study therapy will be calculated based on the number of doses of study drug the patient would have been expected to receive based on the number of treatment days, the specific dosing regimen indicated for the given drug, and the start and stop date and times of the first and last dose of each study drug. Treatment compliance is defined as the number of doses actually received divided by the number of doses expected ($\times 100$) over the time period of first dosing date and time to last dosing date and time.

9.7.5 Efficacy Analyses

Efficacy analyses will be based on the mITT analysis set. *Baseline* for efficacy is defined as the last measurement collected just before the first dose of randomized study drug. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For each efficacy parameter listed below, number and proportion of patients with categories of clinical responses will be presented by treatment groups, and the 2-sided 95% confidence intervals for the percentage of patients with favorable response will be obtained using the Clopper-Pearson method ([Clopper and Pearson, 1934](#)) for each treatment group unless stated otherwise. Due to the small sample size of comparator treatment arm, the between treatment comparison will not be provided.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the clinical response at Day 42 in the CE population. Clinical response can be either cure, failure, or indeterminate, as defined in [Section 9.5.1.1.1](#). For calculation of the 95% confidence interval for the percentage of patients with response of cure, the indeterminate responses will be treated as failures.

9.7.5.2 Secondary Efficacy Parameters

The following are the secondary efficacy parameters:

- Clinical improvement at Day 21 in the mITT and CE Populations
 - Clinical improvement at Day 21 is defined as no worsening of pain from baseline (if present at baseline) (subjective pain and/or point tenderness) and improvement in inflammation (as measured by CRP).
- Clinical response (cure, failure, or indeterminate) at Day 42 in the mITT and micro-mITT Populations

- Clinical response (cure, failure, or indeterminate) at Day 180 in the mITT and CE Populations
- Clinical response (cure, failure, or indeterminate) at Day 365 in the mITT and CE Populations
- Clinical response (cure, failure, or indeterminate) by pathogen at Day 42 and Day 180 in the CE Population.

Clinical responses at Days 180 and 365 are defined and handled in the same way as the primary parameter. For clinical response by pathogen, 95% confidence intervals will be calculated only for pathogens for which sample sizes are greater than 10 in the dalbavancin group.

[REDACTED]

9.7.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it was not present before the date of the first dose of investigational product or was present before the date of the first dose of investigational product and increased in severity during the treatment period. If more than 1 AE is reported before the date of the first dose of investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the treatment period that were also coded to that preferred term.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and causal relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group.

The incidence of common (eg, $\geq 2\%$ of patients in any treatment group) TEAEs, on-therapy SAEs, and AEs leading to premature discontinuation of the investigational product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the test treatment. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

9.7.6.2 *Clinical Laboratory Parameters*

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of patients with PCS postbaseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the patient identification number, study center number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS laboratory values will also be provided.

Patients who meet the potential Hy's law criteria will be summarized for the Safety Population. Supportive tabular displays will also be provided.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (ie, systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature) and changes from baseline values at each visit and at end of study will be presented by treatment group.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline–value criteria detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the patient identification number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS vital sign values will also be provided.



9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

This study is not powered for comparative inferential statistical analyses.

The planned enrollment of 70 patients in the dalbavancin treatment arm will result in a 2-sided 95% confidence interval with the approximate half-width of 11% for the proportion of patients with a clinical cure when the expected proportion is 65%. Higher observed favorable response rates will result in improved precision. The precision for the comparator arm is not estimated due to the small sample size. The comparator arm is intended to provide information on SOC treatment regimens and overall generalizability of study findings, and is not intended to provide a statistically powered comparison of efficacy.

9.7.10 Computer Methods

Statistical analyses will be performed using SAS version 9.3 or higher.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by the Sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IEC and the signature page, signed by the Investigator, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IEC review and approval. However, the IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, and scheduling of visits not in accordance with specifications.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the Sponsor. Protocol deviations must be reported to the Sponsor (either verbally or electronically) in a timely manner from the date of discovery.

Protocol deviations that may impact patient's rights (eg, failure to obtain informed consent prior to initiating study procedures); safety or well-being (eg, deviations that resulted in an SAE, exposure during pregnancy); or the integrity and authenticity of the study data should be reported to the Sponsor within 24 hours, if possible.

The IEC must be notified according to the criteria and time period dictated by the IEC associated with this study.

10.0 **STUDY SPONSORSHIP**

This study is sponsored by Durata Therapeutics International BV, an affiliate of Actavis, Inc.

10.1 **STUDY TERMINATION**

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 **REPORTING AND PUBLICATION**

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and the Sponsor, and will follow the Sponsor's Standard Operating Procedures on publications.

11.0 **INVESTIGATOR OBLIGATIONS**

11.1 **DOCUMENTATION**

The Investigator must provide the following to Durata Therapeutics (an affiliate of Actavis, Inc.), before the start of the study:

- A fully executed contract
- The curricula vitae for the Investigator and all Sub-Investigators, including a copy of each physician's license
- A copy of the original IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IEC, as stated in [Section 9.8](#).
- A copy of the IEC-approved ICF and any supplemental privacy form, if applicable
- A list of the IEC members
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the Investigator
- Financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators. The Investigator and all Sub-Investigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study.

11.2 **PERFORMANCE**

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-Investigators. The investigational products must be stored in a secured place and must be locked. At study initiation, a representative from the Sponsor will inventory the investigational products at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The Sponsor will supply forms on which to record the date the investigational products were received and a dispensing record in which to record each patient's use. All unused investigational products must be returned to the Sponsor. It is the Investigator's responsibility to ensure that patients return their investigational product.

11.4 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by the Sponsor, through the EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to the Sponsor. The Investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local laboratory results), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and patient identification number. Patients' names are not to be transmitted to the Sponsor. The Investigator will keep a master patient list on which the patient identification number and the full name, address, and telephone number of each patient are listed.

12.0 **INVESTIGATOR'S STATEMENT**

I agree to conduct the study in accordance with this protocol (DAL-MD-04, dated 23 Jun 2015) and with all applicable government regulations and good clinical practice guidance.

_____ _____ / _____ / _____
Investigator's Signature Date

Investigator's Name

13.0 **APPENDICES**

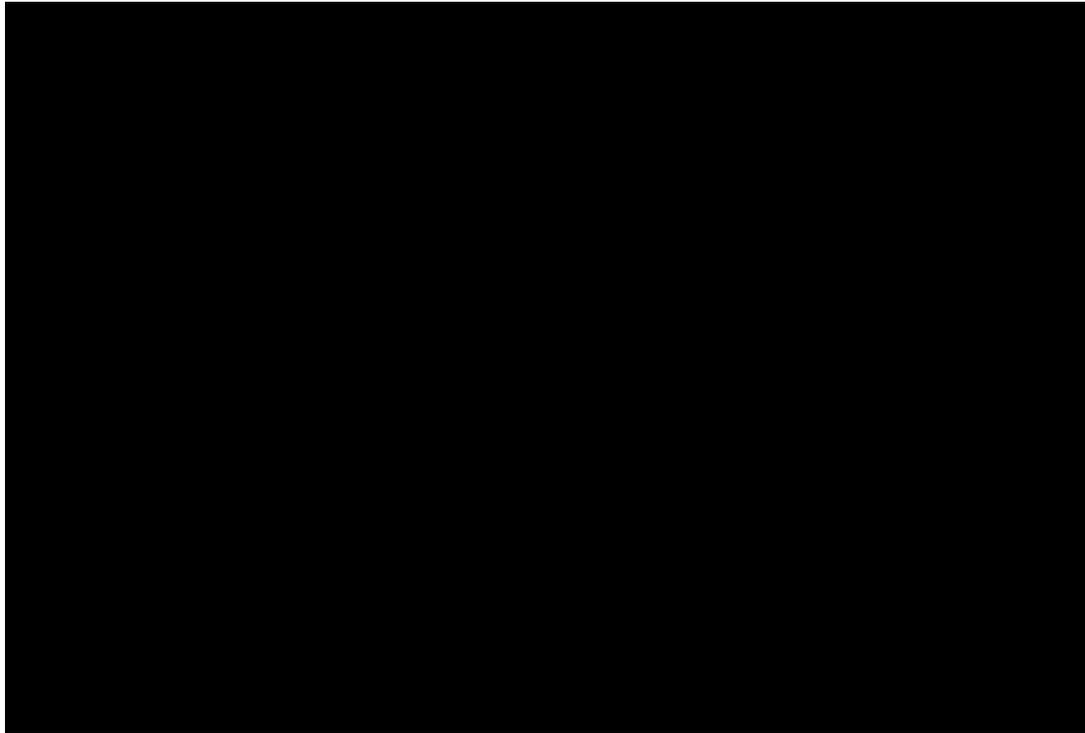
APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's legally authorized representative. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence).
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; the Sponsor; the IEC; another regulatory agency or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IEC may be required)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of consent (eg, "I agree to participate . . .")
- A place for the patient's signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the patient.



APPENDIX III. POTENTIAL DRUG-INDUCED LIVER INJURY/HY'S LAW

IDENTIFICATION

The Investigator is responsible for determining whether a patient meets the following potential Hy's law (PHL) criteria at any point after initiation of study therapy (IV or oral). For a PHL case to meet Hy's Law, the increases from baseline in AST or ALT and total bilirubin values, in the Investigator's clinical judgment, should be temporally related to one another and to the administration of study drug, without an alternative explanation.

PHL

AST or ALT $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ and ALP $< 2 \times \text{ULN}$

If there are increases from baseline in AST or ALT $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$:

- The Investigator must follow the instructions in this appendix
- The investigative site must complete the appropriate screen(s) of the eCRF with the local laboratory test results

FOLLOW-UP AND REPORTING

If the Investigator determines that the patient has not met PHL criteria (has not had increases from baseline in AST or ALT $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ and ALP $< 2 \times \text{ULN}$, at any point after initiation of study drug), the Investigator is to perform follow-up on subsequent laboratory results as required for patient care and per protocol [Section 9.5.2.9.1](#).

If the Investigator determines that the patient has met PHL criteria (has had AST or ALT $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$, and ALP $< 2 \times \text{ULN}$, elevated from baseline at any point after initiation of study drug):

- The Investigator should review the criteria for premature discontinuation of study drug due to elevated liver chemistry values, per protocol [Section 9.3.3](#)
- Any PHL case should be handled as an SAE associated with the use of the drug and reported as an SAE per protocol [Section 9.5.2.5](#) (ie, even before all other possible causes of liver injury have been excluded). It should be promptly reported before doing a full workup on the patient to rule out other etiologies

- The Investigator will investigate the etiology of the event and establish if another explanation/alternative cause other than drug-induced liver injury caused by the study drug is possible. The Sponsor may be contacted to discuss the work-up.
- The investigative site must complete the appropriate screens of the eCRF.

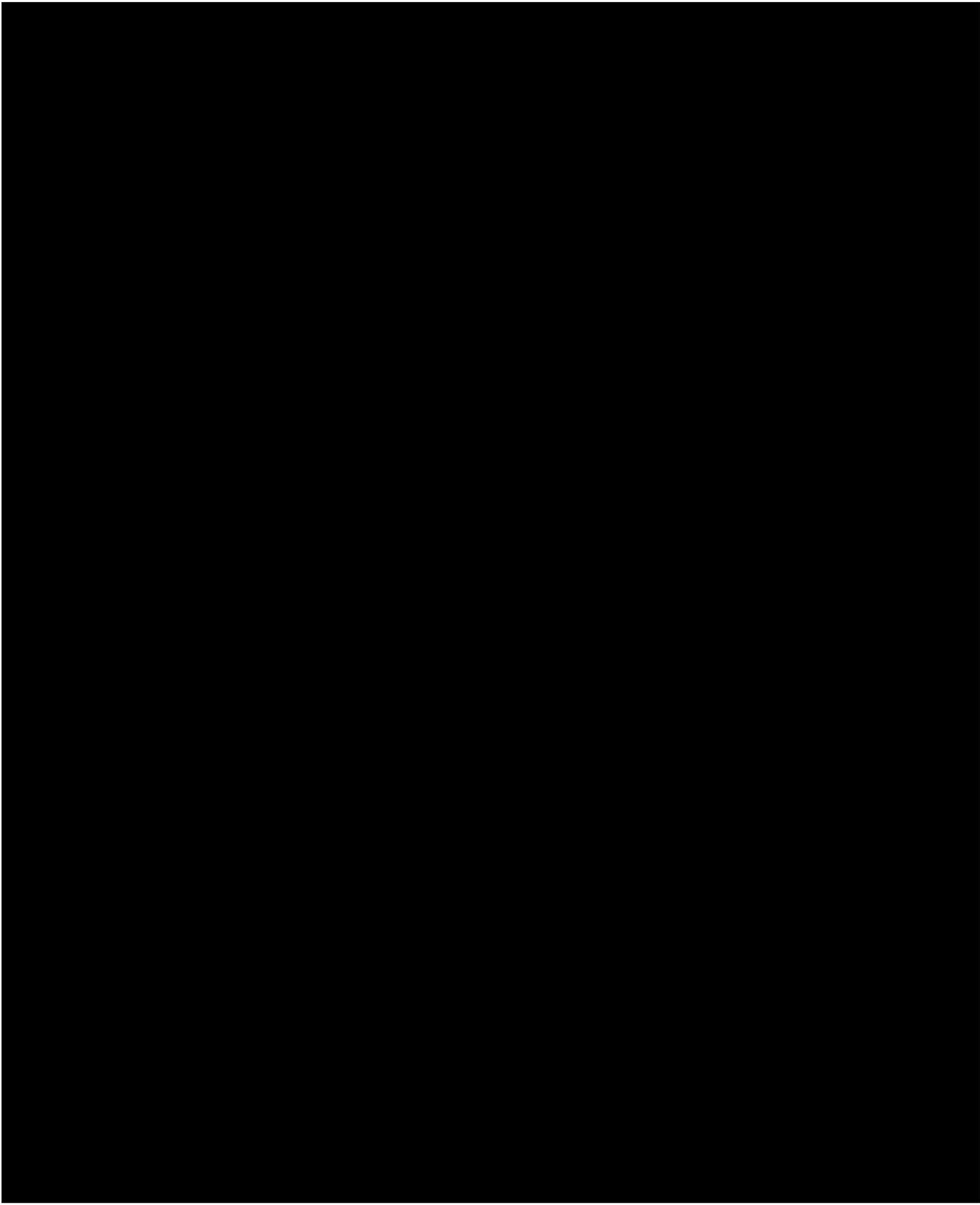
If there is an alternative explanation or the liver chemistry values increased from baseline are not temporally related to one another and to the initiation of study drug, the Investigator should update the PHL SAE to reflect the attributed underlying illness and reassign an appropriate causality assessment, per protocol [Sections 9.5.2.5](#) and [9.5.2.2](#), respectively.

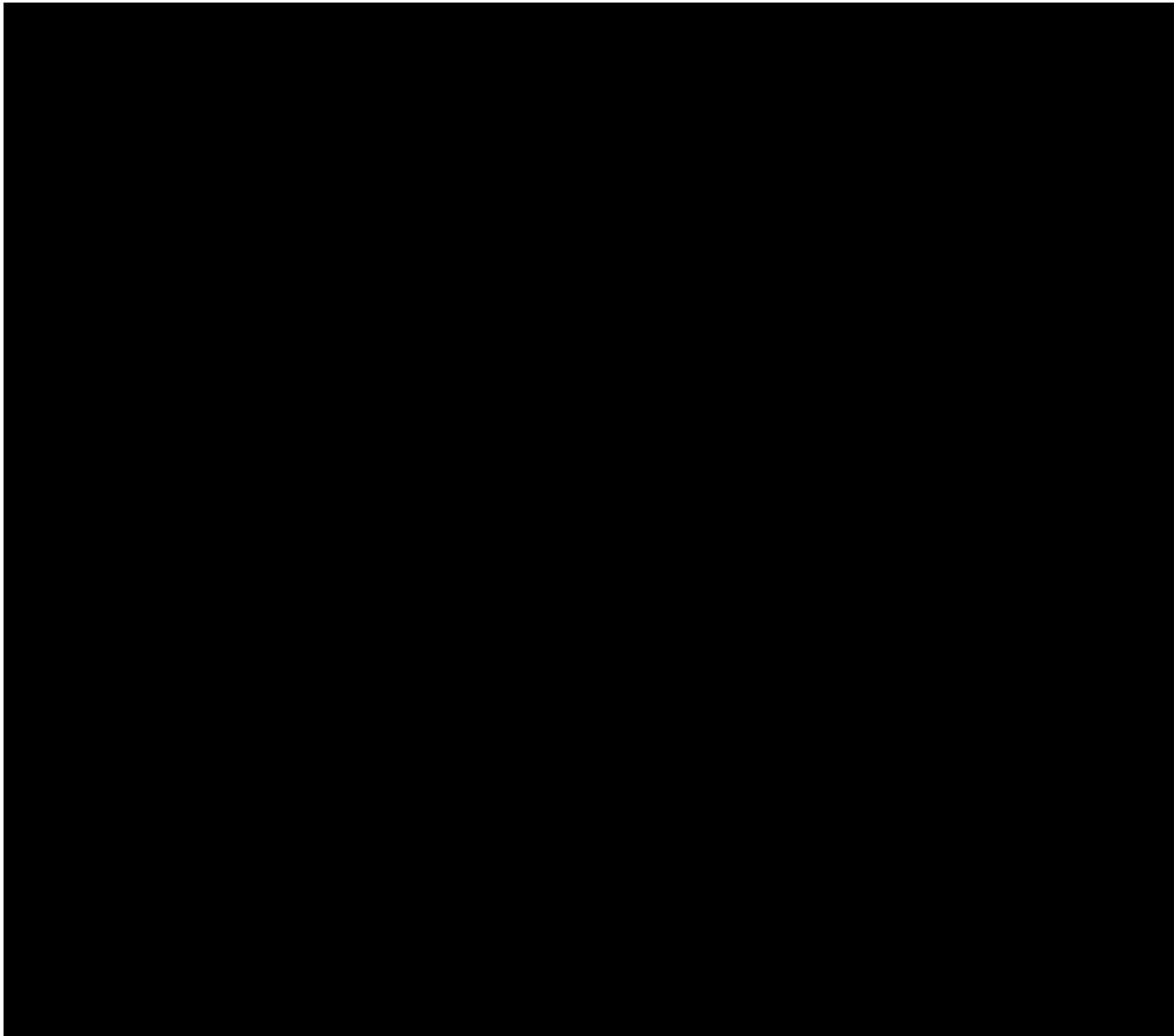
If there is no alternative explanation and the liver chemistry values increased from baseline are temporally related to one another and to the initiation of study drug, the Investigator should update the PHL SAE to a Hy's Law case (reported term 'Hy's Law') and reassign a causality assessment of "related."

If, despite the Investigator's attempts to conduct follow-up and the guidance provided in this appendix, there is an unavoidable delay of > 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.

REFERENCE

US Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: Premarketing clinical evaluation. 2009 Jul. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>. Accessed 2014 Oct 28.





14.0 **LITERATURE CITED**

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