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Study ID: 3026-201-008

Title: A Phase 2, Multicenter, 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: 17 Feb 2017

1.0 TITLE PAGE

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A Phase 2, Multicenter, 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

3026-201-008

Dalbavancin

IND # 60,613

Original Protocol Date: **25 January 2017**
Version 2 Protocol Date: **17 February 2017**

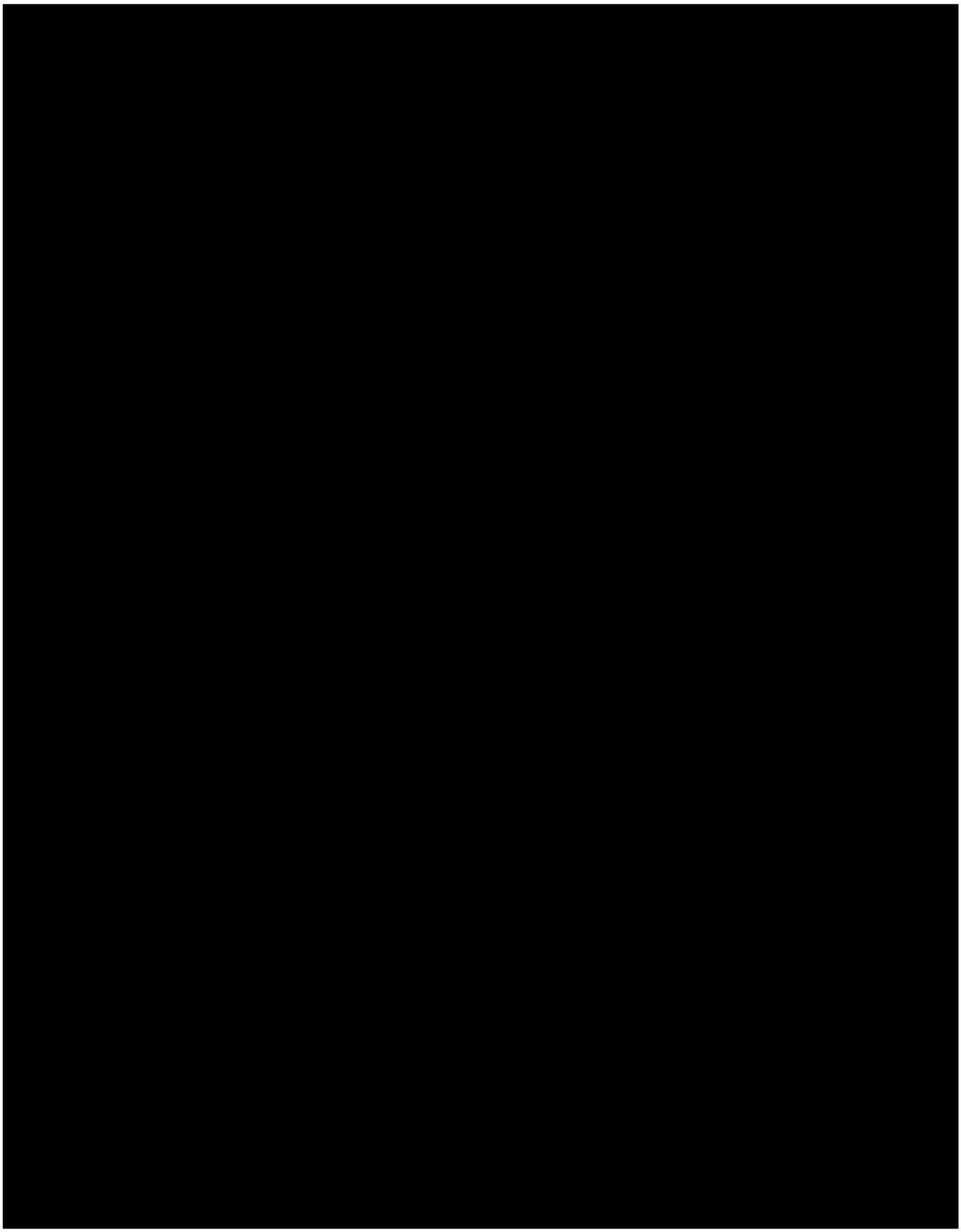
2.0 STUDY 3026-201-008 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study 3026-201-008	
Title of Study	A Phase 2, Multicenter, 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
Study Centers (Country)	Approximately 10 study centers (United States)
Development Phase	2
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 at Day 42 Secondary: • 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 28, Day 180, and Day 365 [redacted]
Methodology	Multicenter, open-label, active-controlled, parallel-arm, randomized, efficacy, and safety study
Number of Patients	Approximately 100 planned (75 in the dalbavancin treatment group and 25 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, and elevated C-reactive protein (CRP) above the upper limit of normal.
Test Product, Dosage, and Mode of Administration	Dalbavancin 1500 mg intravenous (IV) over 30 (± 5) minutes on Day 1 and Day 8 (if creatinine clearance ≥ 30 mL/min or if on regular hemodialysis or peritoneal dialysis) • Dose reduction if creatinine clearance < 30 mL/min (and not receiving regular hemodialysis or peritoneal dialysis): dalbavancin 1000 mg IV over 30 (± 5) minutes on Day 1 and Day 8
Duration of Treatment	Dalbavancin treatment group: 2 doses of dalbavancin: first dose on Day 1 and the second dose on Day 8 Comparator treatment group: 4 to 6 weeks of oral or IV standard of care antibiotic therapy All patients will be followed up for a period of 365 days from the start of therapy (ie, Day 1)

Reference Therapy, Dosage, and Mode of Administration	Standard of care antibiotic (oral or IV) for the treatment of osteomyelitis based on the judgment of the study physician Drugs allowed as concomitant medications • Aztreonam may be administered at randomization for presumed co-infection with a Gram-negative pathogen and can 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.
Criteria for Evaluation	
Primary Outcome Measure	The primary efficacy assessment is the clinical response at Day 42 in the Clinically Evaluable (CE) Population. Clinical response will include assessment of the need for additional antibiotic therapy, presence of purulent discharge/drainage, need for amputation due to progression of infection or due to vascular insufficiency, death (for any reason), or lost to follow-up. 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 treatment group ○ Death (for any reason). • Indeterminate is defined as: ○ Lost to follow-up ○ Amputation due to vascular insufficiency (from initiation of study drug to Day 42).
Secondary Outcome Measures	The following secondary efficacy assessments will be made: • *Clinical improvement at Day 28* in the modified Intent-to-Treat (mITT) and CE Populations will be based on an assessment of pain and/or point tenderness compared to baseline and assessment of inflammation (as measured by CRP). ○ Clinical improvement at Day 28 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 at Day 42, Day 180, and Day 365* will be defined as cure, failure or indeterminate (see Primary Outcome Measure), for the following populations: ○ Clinical response (cure, failure, or indeterminate) at Day 42 in the mITT and microbiological modified Intent-to-Treat (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]	[redacted]
[redacted]	[redacted]
Statistical Methods	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. All safety parameters will be analyzed descriptively. Safety analyses will be based on the Safety Population, a subset of the ITT Population and includes all randomized patients who receive any amount of randomized medication. Efficacy analyses will be based on the mITT, micro-mITT and CE Populations, defined as follows: mITT Population is 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; micro-mITT Population is a subset of the mITT Population and will include patients with a Gram-positive pathogen isolated from blood and/or bone specimen); CE Population is a subset of the mITT Population and will include patients who meet both of the following specific conditions for evaluability: 1) 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; 2) received no more than 1 dose of another (nonstudy) 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. For each efficacy parameter, number and proportion of patients with categories of clinical responses will be presented by treatment groups, and the 2-sided 95% CIs for the percentage of patients with favorable response will be obtained using the Clopper-Pearson method for each treatment group unless stated otherwise. Due to the small sample size of comparator treatment group, the between treatment comparison will not be provided.

[redacted]



3.0 TABLE OF CONTENTS

3.1 LIST OF TABLES

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 the concentration-time curve
CE	clinically evaluable
CFR	Code of Federal Regulations
CFU	colony-forming units
CrCl	creatinine clearance
CRP	C-reactive protein
[redacted]	[redacted]
eCRF	electronic case report form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
FDA	US Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
[redacted]	[redacted]
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous, intravenously
IWRS	interactive web response system
MIC	minimum inhibitory concentration

MIC_{90}	minimum inhibitory concentration to inhibit the growth of 90% of organisms
mITT	modified Intent-to-Treat
micro-mITT	microbiological modified Intent-to-Treat
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
PCS	potentially clinically significant
PHL	potential Hy's Law
PICC	peripherally inserted central catheter
PID	patient identification
PK	pharmacokinetic
RSM	Regional Site Manager
SAE	serious adverse event
SD	standard deviation
SF-12	Short Form-12
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the investigator. A copy of the approval letter will be supplied to the sponsor along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (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 IRBs at the study centers in conformance with CFR, Title 21, Part 56.

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 International Conference on Harmonization (ICH) Guidance on General Considerations for Clinical Trials (ICH-E8; 62 Federal Register [FR] 66113, 17 Dec 1997) and GCP (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 approximately 10 study centers in the United States.

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 IRB, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

7.1 BACKGROUND

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 2009).

Standard treatment for osteomyelitis requires prolonged antibiotic therapy (4 to 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* (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 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.

7.2 DALBAVANCIN

Dalbavancin is a lipoglycopeptide which is highly active against Gram-positive bacteria, including *streptococci*, *S. pneumoniae* and *S. aureus*, including MRSA; the minimum inhibitory concentration to inhibit the growth of 90% of organisms (MIC_{90}) 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 noninferior 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 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.

7.3 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 postdose. Enrolled patients received a single 1000 mg dose of dalbavancin at the appropriate timepoint prior to scheduled surgery. Thirty-one patients 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 MIC_{90} of *S. aureus* through the final sample collection at 336 hours (14 days) (see Table 7-1). The mean bone:plasma area under the concentration-time curve (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 MIC_{90} of *S. aureus* through final sample collection. Similar values were seen in synovial tissue.

Table 7–1. Dalbavancin Tissue Concentrations (Mean ± SD) in Study DUR001-105

Tissue	Postdose Sample Collection Timepoints (Hours [Days])					
	12 [0.5]	24 [1]	72 [3]	168 [7]	240 [10]	336 [14]
Plasma (µg/mL)[a]	85.3 (18.9) N=31	ND	ND	ND	ND	15.3 (4.1) N=31
Synovium (µg/g)[b]	25.0 (0) N=3	17.9 (7.8) N=3	19.5 (4.9) N=3	19.2 (8.9) N=4	25.0 (0) N=2	15.9 (7.9) N=3
Synovial fluid (µg/mL)[b]	22.9 N=1	27.4 (10.8) N=4	19.2 (4.9) N=3	11.6 (3.3) N=2	13.9 (1.0) N=3	6.2 (1.7) N=2
Bone (µg/g)	6.3 (3.1) N=5	5.0 (3.5) N=5	4.6 (3.8) N=5	3.8 (2.7) N=5	3.7 (2.2) N=5	4.1 (1.6) N=5
Skin (µg/g)[b]	19.4 (7.9) N=2	12.5 (6.5) N=3	13.8 (1.4) N=2	15.7 (1.0) N=2	21.6 N=1	13.8 (2.1) N=2

N = number of samples; ND = not detected; SD = standard deviation

a Mean (SD) plasma concentrations in 31 subjects at 772 and 1080 hours were 6.2 (2.4) and 3.4 (1.7), respectively.

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

Source: Dunne 2015

7.4 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 intraperitoneally, 50 mg/kg, every 12 hours) 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 colony-forming units [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 pharmacokinetics 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 MIC_{90} 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 to 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 at Day 42

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 28, Day 180, and Day 365

[redacted]

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This clinical study will be a multicenter, open-label, active-controlled, parallel-arm, randomized, efficacy and safety 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 comparator treatment group will receive treatment with SOC therapy for 4 to 6 weeks. Patients will then be followed up for a period of 365 days (counted from Day 1).

The Schedule of Assessments and Procedures is presented in Table 2–1. Detailed descriptions of each study visit can be found in Section 9.5.5.

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 different dosing schedules.

There will be 2 open-label treatment groups: intravenous (IV) dalbavancin 1500 mg on Day 1 and Day 8, and oral or IV SOC antibiotic for osteomyelitis based on investigator judgment for 4 to 6 weeks. The 2 groups will be randomized in a 3:1 ratio (75 patients in the dalbavancin treatment group and 25 patients in the comparator treatment group).

The comparator treatment group will serve as a contemporaneous illustration of typical SOC regimens used at the study sites, and to help assess generalizability of study findings, since the study will be done at approximately 10 sites in the United States. A small comparator group (n = 25) 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 timepoints 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 of age
2. A diagnosis of osteomyelitis (first episode) defined by:
   - Pain or point tenderness upon palpation or probing to bone

   AND

- Plain film radiograph or magnetic resonance imaging (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

AND

- Elevated C-reactive protein (CRP) (low sensitivity) above the upper limit of normal (ULN) (reference range for low sensitivity CRP, 3-10 mg/L)

3. A signed and dated written informed consent document indicating that the patient (or a legally authorized representative) has been informed of all pertinent aspects of the study.

4. Patients 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

Patients 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 noncontiguous 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/mm^3, 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

infection with a CD4 cell count < 200 cells/mm^3 or with a past or current acquired immunodeficiency syndrome-defining condition and unknown CD4 count.

7. Evidence of Gram-negative bacteria by Gram stain from a bone specimen 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 minimum inhibitory concentration [MIC] > 0.25 µg/mL) or vancomycin (vancomycin MIC > 2 µg/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 (premenopausal females only) or after admission (prior to dosing)

18. Sexually active females of childbearing potential who are unwilling or unable to practice complete abstinence or simultaneously use 2 effective contraceptive methods from the following list, from at least the first dose of study drug until the last pregnancy test:

    a. A barrier (condoms, diaphragm or cervical cap) with spermicide

    b. A second, different barrier method (condoms, diaphragm or cervical cap)

    c. Oral or similar contraceptive, which includes, but is not limited to: injectable implanted, or patch hormone therapy, and intrauterine device

d. Documented surgical sterilization at least 4 weeks prior to Baseline

e. Partner vasectomy at least 6 months prior to Baseline

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 the sponsor, 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 Day 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 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 the 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 the 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 the 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. If a patient withdraws from the study prematurely prior to Day 28, a plain film radiograph should be obtained at time of discontinuation. 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 from the study 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 (ie, creatinine clearance [CrCl] ≥ 30 mL/min) (and patients receiving regular hemodialysis or peritoneal dialysis): dalbavancin 1500 mg IV over 30 (± 5) minutes on Day 1 and Day 8.
- Chronic renal insufficiency (with a serum CrCl of < 30 mL/min and not receiving regular hemodialysis or peritoneal dialysis): dalbavancin 1000 mg IV over 30 (± 5) minutes on Day 1 and Day 8.

9.4.1.2 Comparator Treatment Group

Patients randomized to the comparator treatment group will receive an oral or IV antibiotic consistent with SOC for osteomyelitis based on investigator judgment. The duration of treatment will be 4 to 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 can 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.

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

9.4.1.4 Duration of Treatment

The total duration of study therapy will be 2 doses of dalbavancin given 1 week apart, or 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 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 (PID) 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. 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

After a patient signs the ICF, study personnel will register the patient in the interactive web response system (IWRS), and the system will assign the patient a sequential, unique 9-digit PID number consisting of a 3-digit protocol number followed by a 3-digit study center 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 PID number will be used to identify the patient at all phases of the study.

If, after review of the inclusion/exclusion criteria, it is determined that the patient is eligible to enter the study, the patient will be randomized to receive either a 2-dose regimen of dalbavancin or 4 to 6 weeks of SOC antibiotic therapy in accordance with Section 9.4.1.2 in a 3:1 allocation ratio.

A patient is considered randomized when study personnel receive the treatment assignment associated with the patient entered into the IWRS. Study centers will dispense investigational product according to the IWRS instructions. Investigational product will be dispensed according to IWRS instructions at each dispensing visit (Day 1 and Day 8 for dalbavancin).

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 2-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 pharmacokinetic (PK) modeling (Dunne 2015).

- The PK/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 and Craig 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 MIC_{90} 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 IV 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 comparator treatment group is expected to be 4 to 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

Estimated Creatinine Clearance (mL/min)[a]	*Recommended Dosage Regimen*
≥ 30 and patients receiving regular hemodialysis or peritoneal dialysis	No adjustment: 1500 mg IV (over 30 minutes ± 5 minutes) on Day 1 and Day 8
< 30	1000 mg IV (over 30 minutes ± 5 minutes) on Day 1 and Day 8

[a] As calculated using the Cockcroft-Gault formula.
IV = intravenous

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.

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

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

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 IV 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 can 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.

Note: Patients may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the targeted examination of the infection site (see Section 9.5.2.12).

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

The primary efficacy assessment is the clinical response at Day 42 in the Clinically Evaluable (CE) Population (see Section 9.7.5.1).

Clinical response will include assessment of the need for additional antibiotic therapy, presence of purulent discharge/drainage, need for amputation due to progression of infection or due to vascular insufficiency, death (for any reason), or lost to follow-up.

Definition of clinical response

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 treatment group
    - Death (for any reason).
- Indeterminate is defined as:
    - Lost to follow-up
    - Amputation due to vascular insufficiency (from initiation of study drug to Day 42).

9.5.1.1.2 Secondary Efficacy Assessments

The following secondary efficacy assessments will be made:

- *Clinical improvement at Day 28* in the modified Intent-to-Treat (mITT) and CE Populations will be based on an assessment of pain and/or point tenderness compared to baseline and assessment of inflammation (as measured by CRP).

- Clinical improvement at Day 28 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 at Day 42, Day 180, and Day 365* will be defined as cure, failure or indeterminate (see Section 9.5.1.1.1 for definitions), for the following populations:

  - Clinical response (cure, failure, or indeterminate) at Day 42 in the mITT and microbiological modified Intent-to-Treat (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]

[redacted]

[redacted]

*9.5.1.3 **Microbiological Assessments***

9.5.1.3.1 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 a 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

9.5.2.1.1 Definition of 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 an 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 eCRF 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 AE unless it is an SAE 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 group
- 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 9.5.2.1.2)
- 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).

9.5.2.1.2 Abnormal Test Findings

An abnormal objective test finding (eg, 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 (eg, 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 AE due to an abnormal lab test finding should be noted in the eCRF.

9.5.2.2 Causality Assessment

For each AE (serious and nonserious), 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 eCRF, 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

9.5.2.4.1 Definition of a Serious Adverse Event

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, ie, 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.

9.5.2.4.2 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 (eg, 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 (eg, 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 (eg, for work-up of persistent pretreatment laboratory abnormality)
- Social admission (eg, patient has no place to sleep)
- Administrative admission (eg, for yearly physical exam)
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery). Preplanned 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 noninvasive 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, ie, 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 Allergan 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 the following number:

[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 (eg, 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 Allergan 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.

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 (PHL) 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 (PHL 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 PHL) to the SAE/Pregnancy fax number stated in Section 9.5.2.6, even if no AE has occurred. The eCRF for PHL 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 less 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: Absolute and differential white blood cell count, neutrophils (absolute count and %), immature neutrophils (bands; %), lymphocytes (absolute count and %), monocytes (absolute count and %), eosinophils (absolute count and %), basophils (absolute count and %), erythrocyte count, hematocrit, hemoglobin, platelet count

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

Other: CRP, erythrocyte sedimentation rate (ESR), pregnancy test (serum or urine)

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.

The volume of blood to be taken for the various laboratory assessments will be specified in the Laboratory Manual.

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 general appearance, examination of head, eyes, ears, nose, throat, neck, skin, heart lungs, abdomen, neurologic system, extremities, height, and body weight) will be conducted at Baseline by a professionally trained physician or health professional licensed to perform physical examinations.

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.

9.5.2.12 Targeted Examination of Infection Site

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

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.

9.5.3 Dalbavancin Concentration Measurements

Blood samples for the determination of dalbavancin in plasma will be collected according to the Schedule of Assessments and Procedures (Table 2–1) as follows:

- Day 1 (2-4 hours after start of infusion)
- Day 8 (predose and 2-4 hours after start of infusion)

- Day 28 (at time of clinic visit; the PK collection date and time must be recorded in the eCRF)
- Day 42 (at time of clinic visit; the PK collection date and time must be recorded in the eCRF).

Blood collection tubes for PK sampling will be provided by the central laboratory. The PK sample collection, labeling, processing, storage, and shipment instructions will be provided in the Laboratory Manual.

In addition, patients who receive dalbavancin who subsequently undergo bone surgery may have the option to have dalbavancin levels assessed in bone and related tissue.

[redacted]

9.5.5 Schedule of Assessments

The schedule of study assessments and procedures is tabulated by study day in Table 2–1. The descriptions of the assessments and procedures to be performed at each visit are provided below.

9.5.5.1 Baseline

Baseline procedures must be completed within 24 hours before the first dose of study drug is administered. Any protocol-required eligibility laboratory evaluations already done as part of the patient's regular medical care within 24 hours of the start of the study drug on Study Day 1 do not have to be repeated to determine patient eligibility.

At Baseline, informed consent will be obtained, a review of inclusion/exclusion criteria will be conducted to determine the patient's eligibility for enrollment, and study procedures will be reviewed with the patient and/or the legally authorized representative (if applicable). After signing the ICF, the patient will be assigned a unique PID number (see Section 9.4.3). If, after review of the inclusion/exclusion criteria, it is determined that the patient is eligible to enter the study, the patient will be randomized according to randomization procedures in Section 9.4.3.

At Baseline, the following procedures will be performed:

- Obtain written informed consent per Section 5.3.
- Access IWRS and assign a unique PID number to the patient (Section 9.4.3).
- Verify that inclusion criteria are met and none of the exclusion criteria apply.
- Obtain information on patient demographics, medical history, and surgical history including all active conditions and all conditions diagnosed within the previous 3 months.

- Perform complete physical examination, including general appearance, examination of head, eyes, ears, nose, throat, neck, skin, heart, lungs, abdomen, neurologic system, extremities, height, and body weight. If height or weight is not obtainable (eg, patient is immobilized), use the last known or stated height and weight.

- Conduct a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.

- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).

- Record medication history: prior medications, including antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the-counter medications (eg, vitamins, herbal medications), and parenteral nutrition taken or received within 30 days of first dose of IV study drug.

- Record previous nondrug adjunctive therapy.

- Laboratory assessments:

    - Collect blood samples for serum chemistry, hematology, CRP, and ESR per Section 9.5.2.9.

    - Collect blood or urine sample for pregnancy test (females of childbearing potential only, including those who are less than 2 years postmenopausal); ensure test is negative before randomization.

    - Collect a 3-mL serum sample for use in retrospective safety assessments or exploratory analyses, as needed (banked serum sample).

    - Collect peripheral blood sample for aerobic and anaerobic cultures, from 2 separate venipuncture sites (4 tubes of blood to be collected). Blood cultures should be repeated upon knowledge of a positive result at Baseline until sterilization is confirmed. 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 time of treatment discontinuation or for determination of treatment failure.

- Bone biopsy to be conducted if clinically appropriate. Obtain histology (if sufficient specimen), Gram stain, aerobic and anaerobic culture, and susceptibility of organisms isolated from the bone specimen at Baseline if sampling is performed as clinically indicated. Suitable methods of collection include bone biopsy, needle aspiration, or drilling.

- MRI (if plain film radiography results are inconclusive)

- Plain film radiography

- Record any AEs (all AEs should be recorded on the eCRF from the time the patient signs the ICF until the final protocol-defined study visit; see Section 9.5.2.1).
- Randomize patient to treatment groups after verifying that the patient meets all study inclusion criteria and no exclusion criteria.
- Collect Health Resource Utilization data (or at Day 1)
- [redacted]
- Schedule next visit: Study Day 1 (this may be the same day as the Baseline assessments were conducted).

*9.5.5.2 **Study Day 1***

Study Day 1 is the calendar day that study drug is first administered. Baseline assessments may be conducted on the same day as, but before, the first dose of study drug, including:

- [redacted]

All Study Day 1 procedures described below are to be conducted after at least 1 dose of study drug (unless otherwise indicated).

- Administer dalbavancin (if in dalbavancin group) or comparator (if in comparator group).
- Document investigational product and SOC treatment compliance.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Record concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Collect Health Resource Utilization data (if not collected at baseline visit); the data can be collected before or after study drug administration.

In addition, for patients in the dalbavancin group:

- Collect a blood sample for determination of dalbavancin in plasma, 2-4 hours after the start of the dalbavancin infusion.
- Schedule next visit: Study Day 8 (within 7 days of Study Day 1).

*9.5.5.3 **Study Day 8***

The patient is to return to the clinic on Study Day 8 when the following procedures and evaluations will be performed:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Collect blood sample for hematology, serum chemistry, CRP, ESR, per Section 9.5.2.9.
- Collect a blood sample for determination of dalbavancin in plasma at predose and 2-4 hours after the start of the dalbavancin infusion (dalbavancin group only).
- Administer second dose of dalbavancin, if in dalbavancin group (after infection site assessment).
- Administer comparator (if in comparator group) according to the product's label instructions (after infection site assessment).
- Document investigational product and SOC treatment compliance.
- Record new concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Collect Health Resource Utilization data.
- [redacted]
- Schedule next visit: Study Day 21 (± 1 day).

*9.5.5.4 **Study Day 21***

Study Day 21 (± 1 day) visit must occur within 1 day of the patient's 21st day in the study. At this visit, the following procedures and evaluations will be performed:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Administer comparator (if in comparator group) according to the product's labeling instructions (after infection site assessment).

- Document SOC treatment compliance (comparator group only).
- Record new concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Collect Health Resource Utilization data.
- [redacted]
- Schedule next visit: Study Day 28 (± 2 days).

*9.5.5.5 **Study Day 28***

Study Day 28 (± 2 days) visit must occur within 2 days of the patient's 28th day in the study, when the following procedures and evaluations will be performed:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Laboratory assessments:
    - Collect blood samples for serum chemistry, hematology, CRP, ESR per Section 9.5.2.9.
    - Collect blood or urine sample for pregnancy test (females of childbearing potential only, including those who are less than 2 years postmenopausal).
    - Collect a 3-mL serum sample for use in retrospective safety assessments or exploratory analyses, as needed (banked serum sample).
    - For patients in the dalbavancin group only: collect a blood sample for determination of dalbavancin in plasma when the patient is in the clinic. Record the collection date and time.
- Plain film radiography
- Administer comparator (if in comparator group) and, if applicable, according to the product's labeling instructions (after infection site assessment).
- Document SOC treatment compliance (comparator group only).
- Record new concomitant medications and concomitant nondrug adjunctive therapy.

- Review and record AEs and SAEs.
- Collect Health Resource Utilization data.
- [redacted]
- Conduct an assessment of clinical improvement (see Section 9.5.1.1.2).
- Schedule next visit: Study Day 42 (± 3 days).

*9.5.5.6 **Study Day 42***

Study Day 42 (± 3 days) visit must occur within 3 days of the patient's 42nd day in the study, when the following procedures and evaluations will be performed:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Laboratory assessments:
    - Collect blood samples for CRP and ESR.
    - Collect blood or urine sample for pregnancy test (females of childbearing potential only, including those who are fewer than 2 years postmenopausal).
    - For patients in the dalbavancin group only: collect a blood sample for determination of dalbavancin in plasma when the patient is in the clinic. Record the collection date and time.
- Plain film radiography
- Administer comparator, if in comparator group and, if applicable, according to the product's labeling instructions (after infection site assessment).
- Document SOC treatment compliance (comparator group only).
- Record new concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Collect Health Resource Utilization data.
- [redacted].
- [redacted]

- [redacted]
- Conduct an assessment of clinical response (see Section 9.5.1.1.1).
- Schedule next visit: Study Day 180 (±7 days).

*9.5.5.7 **Study Day 180***

Study Day 180 (± 7 days) visit must occur within 1 week of the patient's 180th day in the study, when the following procedures and evaluations will be performed:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Collect blood sample for CRP and ESR.
- Plain film radiography
- Record new concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Collect Health Resource Utilization data.
- Conduct an assessment of clinical response (see Section 9.5.1.1.1).
- Schedule next visit: Study Day 365 (±14 days).

*9.5.5.8 **Study Day 365***

Study Day 365 (± 14 days) visit must occur within 2 weeks of the patient's 365th day in the study, when the following procedures and evaluations will be performed:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic]).
- Record new concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Collect Health Resource Utilization data.

- Conduct an assessment of clinical response (see Section 9.5.1.1.1).

9.5.5.9 Early Termination Visit

If a patient discontinues from the study prematurely, the following procedures and assessments will be carried out at an Early Termination Visit:

- Perform a targeted examination of infection site. The same medically trained individual should perform all assessments, if possible. Patient may not receive pain medication, including ibuprofen and acetaminophen, within the 4 hours preceding the assessment.
- Record vital signs (blood pressure and pulse rate after patient has been sitting for at least 5 minutes, respiratory rate, temperature [oral, rectal, or tympanic])
- Laboratory assessments:
    - Collect blood samples for serum chemistry, hematology, CRP, ESR per Section 9.5.2.9.
    - Collect blood or urine sample for pregnancy test (females of childbearing potential only, including those who are less than 2 years postmenopausal).
- If the patient discontinues the study prematurely prior to Day 28, a plain film radiography should be obtained at time of discontinuation.
- Record new concomitant medications and concomitant nondrug adjunctive therapy.
- Review and record AEs and SAEs.
- Document investigational product and SOC treatment compliance, where applicable.
- Collect Health Resource Utilization data.
- [redacted].
- [redacted]
- [redacted].

Any clinical findings obtained during the final examination or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, 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.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Recording and Documentation

Data collection will involve the use of the Allergan 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, 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

Definitions of the Analysis Populations considered in the statistical analysis of the study are provided below.

9.7.1.1 Screened Population

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

9.7.1.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study, regardless of whether or not they receive study treatment.

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; see Section 9.3.1). 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 Microbiological Modified Intent-to-Treat Population

The 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.

9.7.1.6 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 (nonstudy) 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 nonstudy systemic antibacterial treatment for the treatment of osteomyelitis from initiation of study drug through the outcome assessment visit will be assessed as EVALUABLE FAILURES]

9.7.2 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 or comparator product. Concomitant medication is defined as any medication started on or after the date of the first dose of investigational product or comparator product. Any prior medications stopped more than 3 days before the date of the first dose of investigational or comparator product and any concomitant medications started after the date of the last dose of investigational or comparator 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, standard deviation (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 (× 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 CIs will be 2-sided 95% CIs, 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% CIs 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 group, the between treatment comparison will not be provided.

9.7.5.1 Primary Efficacy Parameter

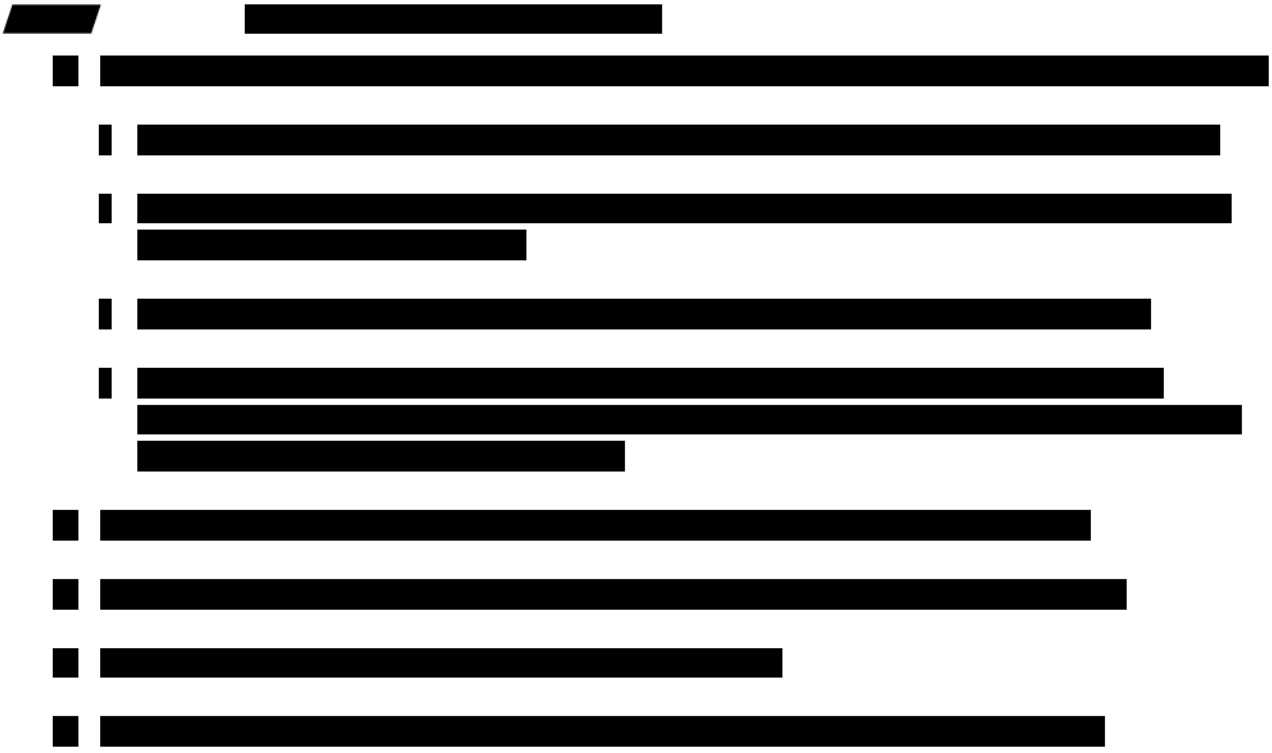
The primary efficacy parameter is the clinical response at Day 42 in the CE Population. Clinical response can be either cure, failure, or indeterminate, as defined in Section 9.5.1.1.1. For calculation of the 95% CI for the percentage of patients with response of cure, the indeterminate responses will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

9.7.5.2 Secondary Efficacy Parameters

The following are the secondary efficacy parameters:

- Clinical improvement at Day 28 in the mITT and CE Populations
    - Clinical improvement at Day 28 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 Day 180 and Day 365 are defined and handled in the same way as the primary parameter. For clinical response by pathogen, 95% CIs 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 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, ≥ 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 timepoint 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 PID 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 PHL 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, and 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 PID 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.

9.7.7 Pharmacokinetic Analyses

Descriptive summary statistics will be provided for dalbavancin PK parameters.

9.7.8 Health Economics and Outcomes Research Analyses

These analyses are described in the efficacy analysis section, please refer to Section 9.7.5.3.

9.7.9 Interim Analysis

No interim analysis is planned for this study.

9.7.10 Determination of Sample Size

This study is not powered for comparative inferential statistical analyses.

Approximately 100 patients are planned to be enrolled (75 in the dalbavancin treatment group and 25 in the comparator treatment group). The planned enrollment of 75 patients in the dalbavancin treatment group will result in a 2-sided 95% CI 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 group is not estimated due to the small sample size. The comparator group 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.

9.7.11 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 IRB 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 IRB review and approval. However, the IRB 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 IRB 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 timepoints, 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 IRB must be notified according to the criteria and time period dictated by the IRB associated with this study.

10.0 STUDY SPONSORSHIP

This study is sponsored by Allergan Sales, LLC.

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 Allergan Sales, LLC., before the start of the study:

- A fully executed contract
- The curricula vitae for the investigator and all subinvestigators, including a copy of each physician's license
- A copy of the original IRB 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 IRB, as stated in Section 9.8.
- A copy of the IRB-approved ICF and any supplemental privacy form, if applicable
- A list of the IRB 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 subinvestigators. The investigator and all subinvestigators 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 subinvestigators. 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 a PID number. Patients' names are not to be transmitted to the sponsor. The investigator will keep a master patient list on which the PID 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 (3026-201-008, dated 17 February 2017) 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 IRB; 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 IRB 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 II. CONTACT INFORMATION

Contact information for the sponsor personnel is as follows:

[redacted]

Contact information for the sponsor personnel is maintained in the Study Reference Manual.

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 ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN **and** ALP < 2 × ULN

If there are increases from baseline in AST or ALT ≥ 3 × ULN **and** total bilirubin ≥ 2 × 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 ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and ALP < 2 × 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 9.5.2.8.

If the investigator determines that the patient has met PHL criteria (has had AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, and ALP < 2 × 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.

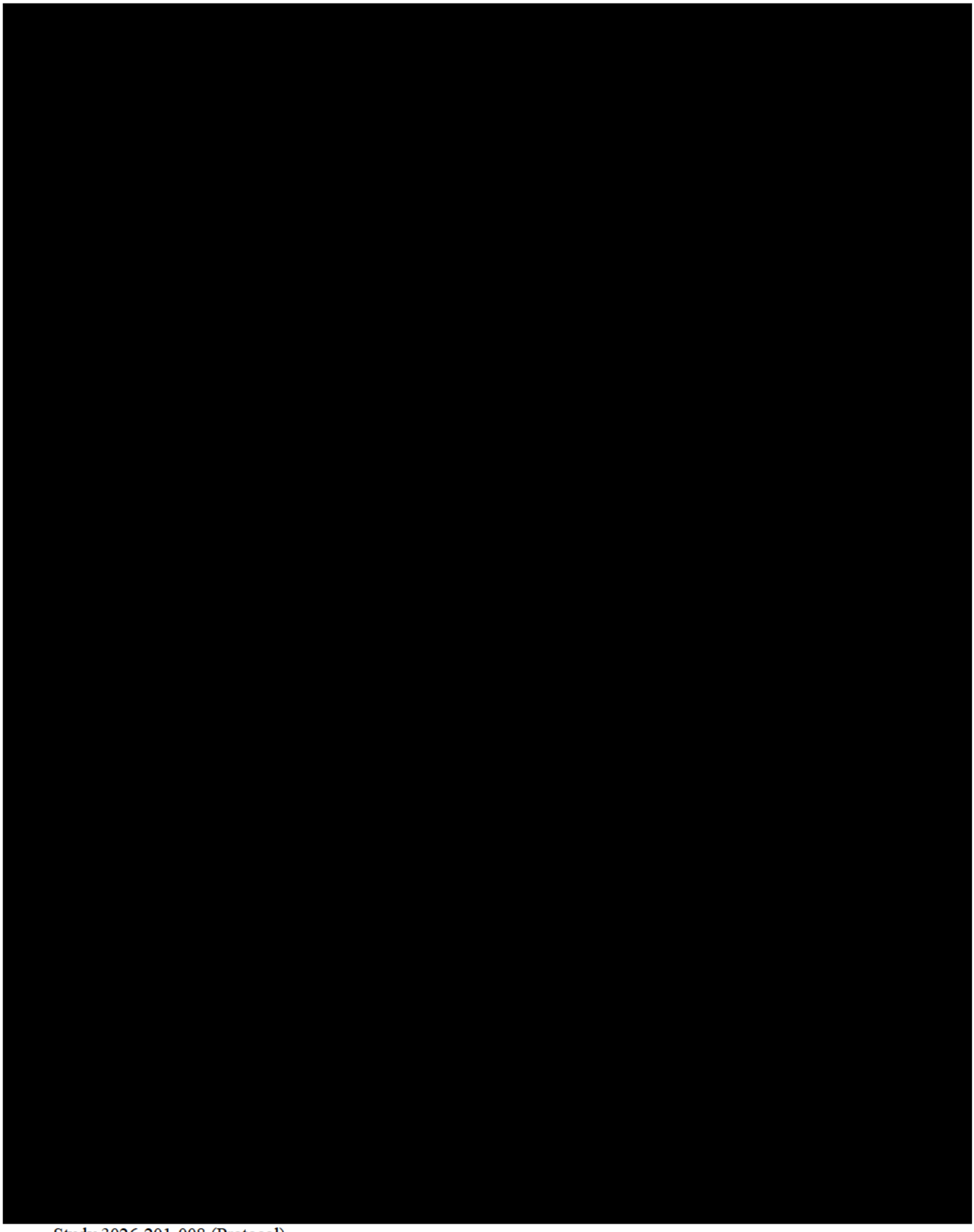
If there is an alternative explanation or the liver chemistry values increased from baseline are not temporally related to one another and to the initiation of study drug, the investigator should update the PHL SAE to reflect the attributed underlying illness and reassign an appropriate causality assessment,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

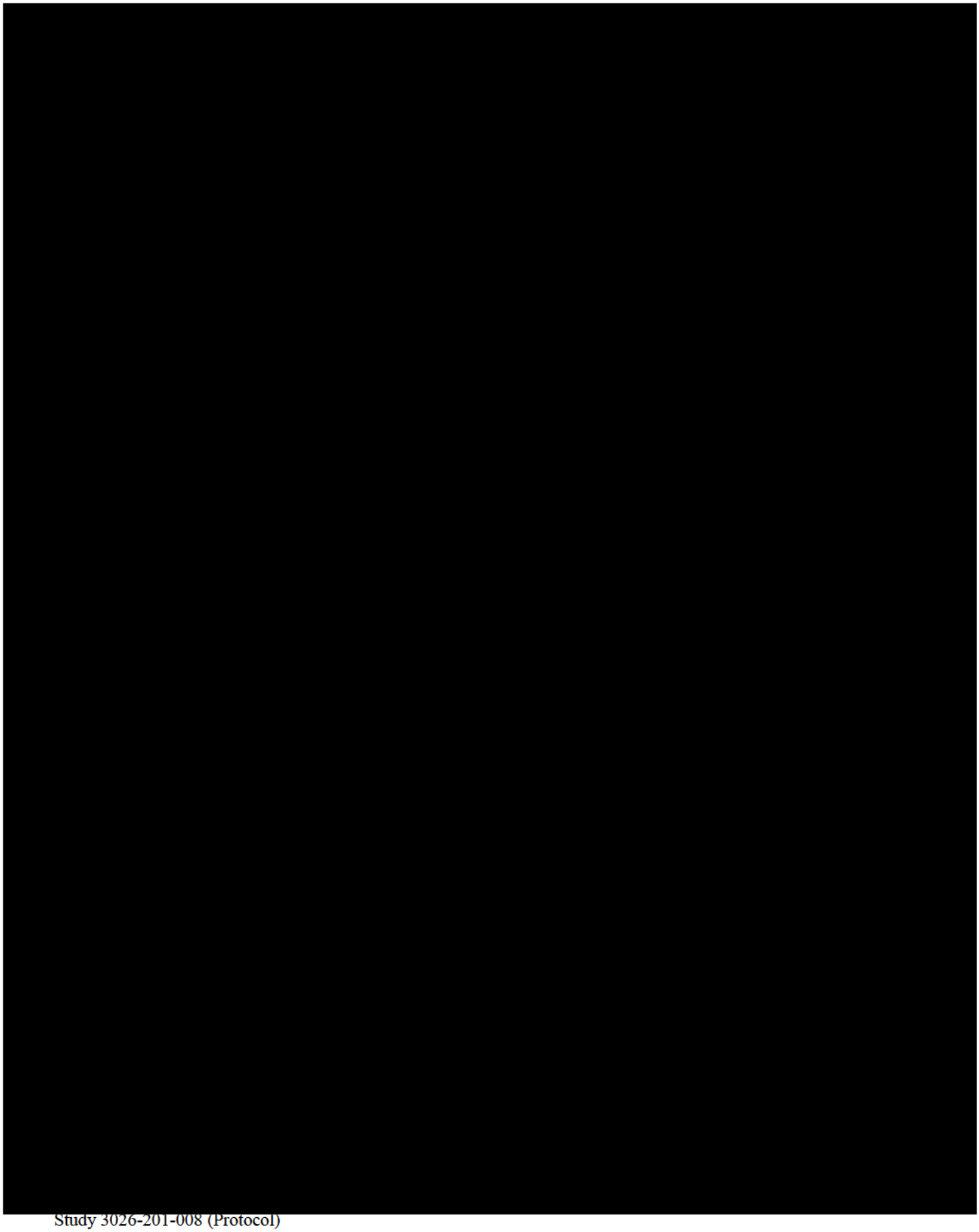
If there is no alternative explanation and the liver chemistry values increased from baseline are temporally related to one another and to the initiation of study drug, the investigator should update the PHL SAE to a Hy's Law case (reported term 'Hy's Law') and reassign a causality assessment of "related."

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.





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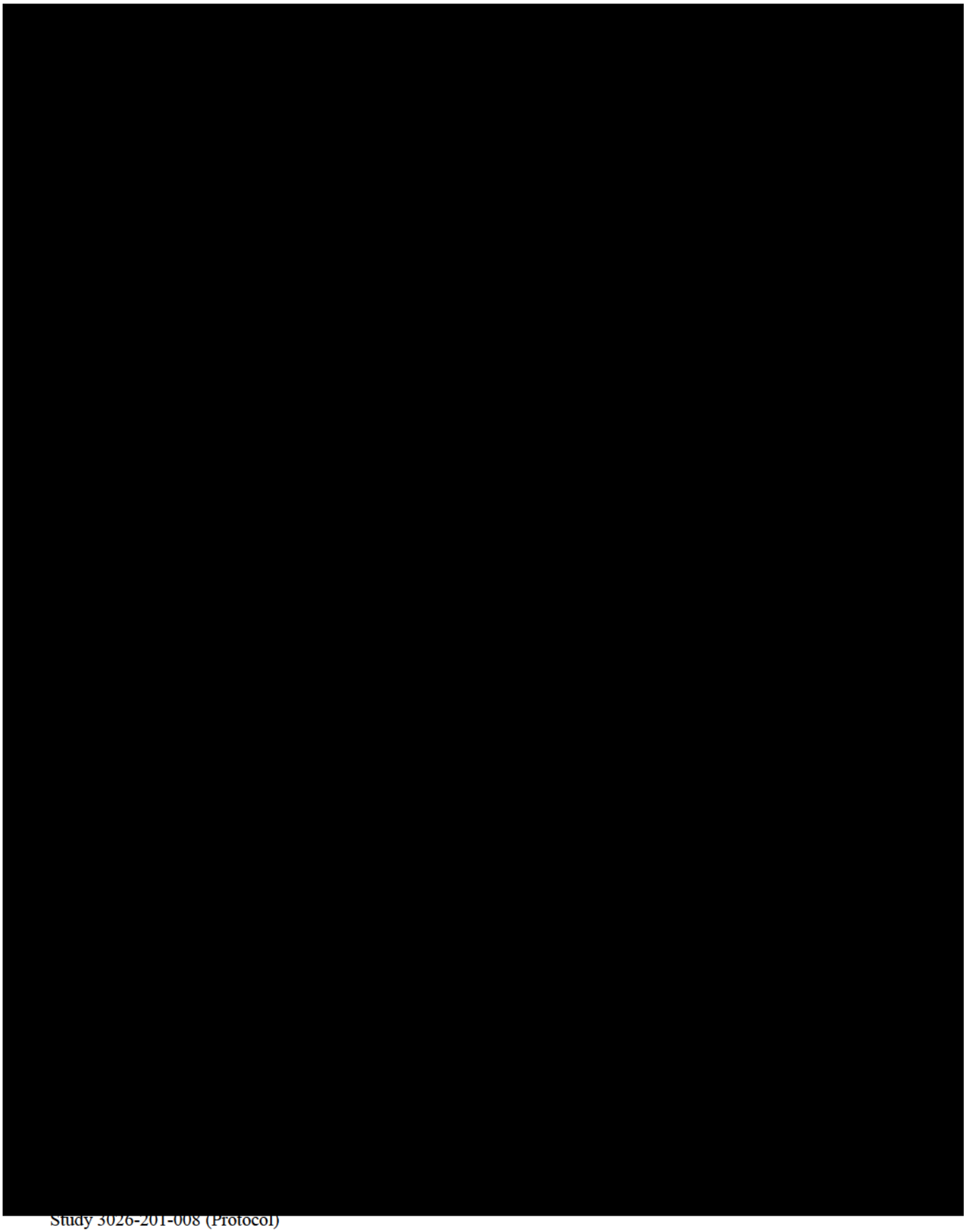

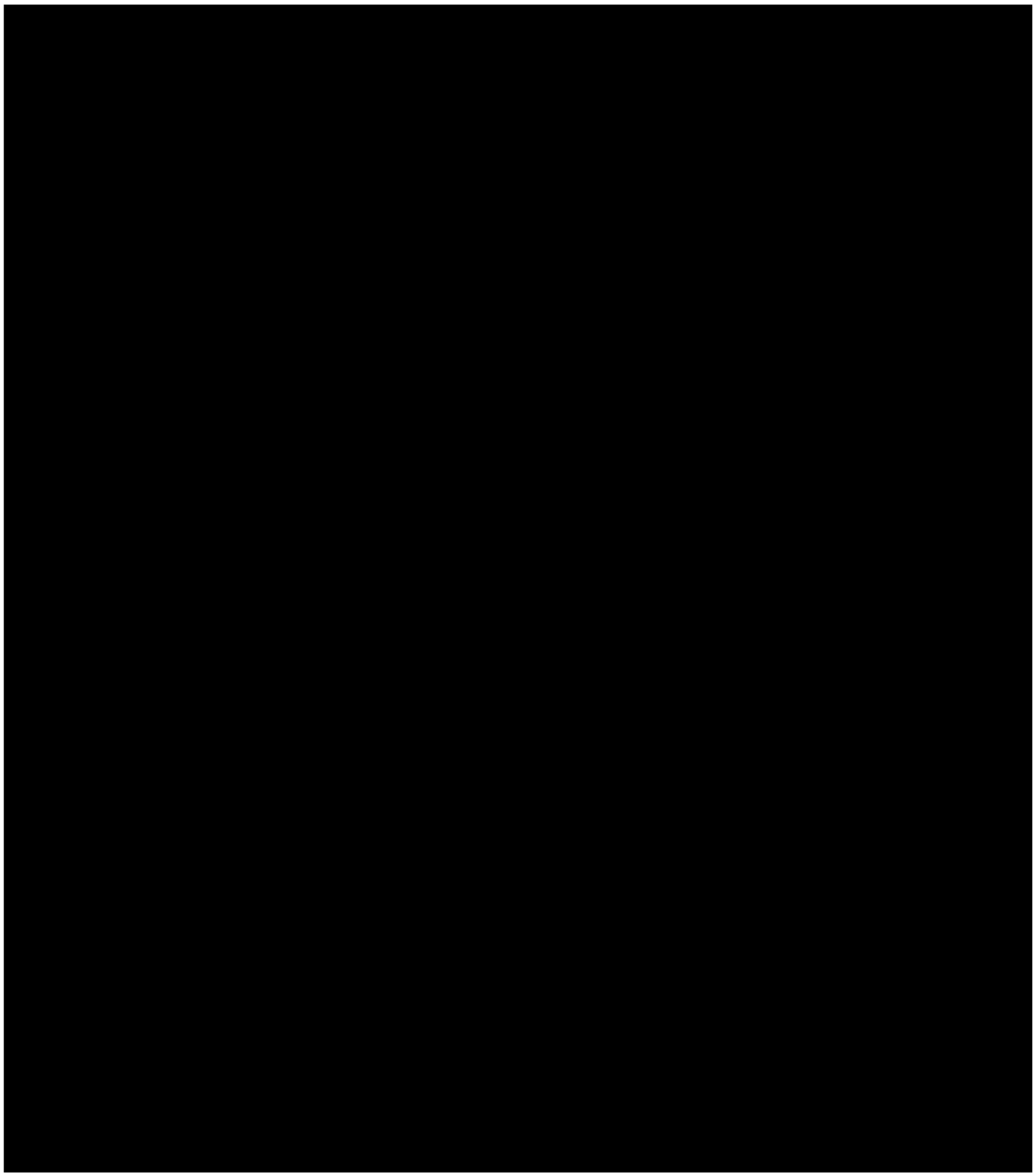

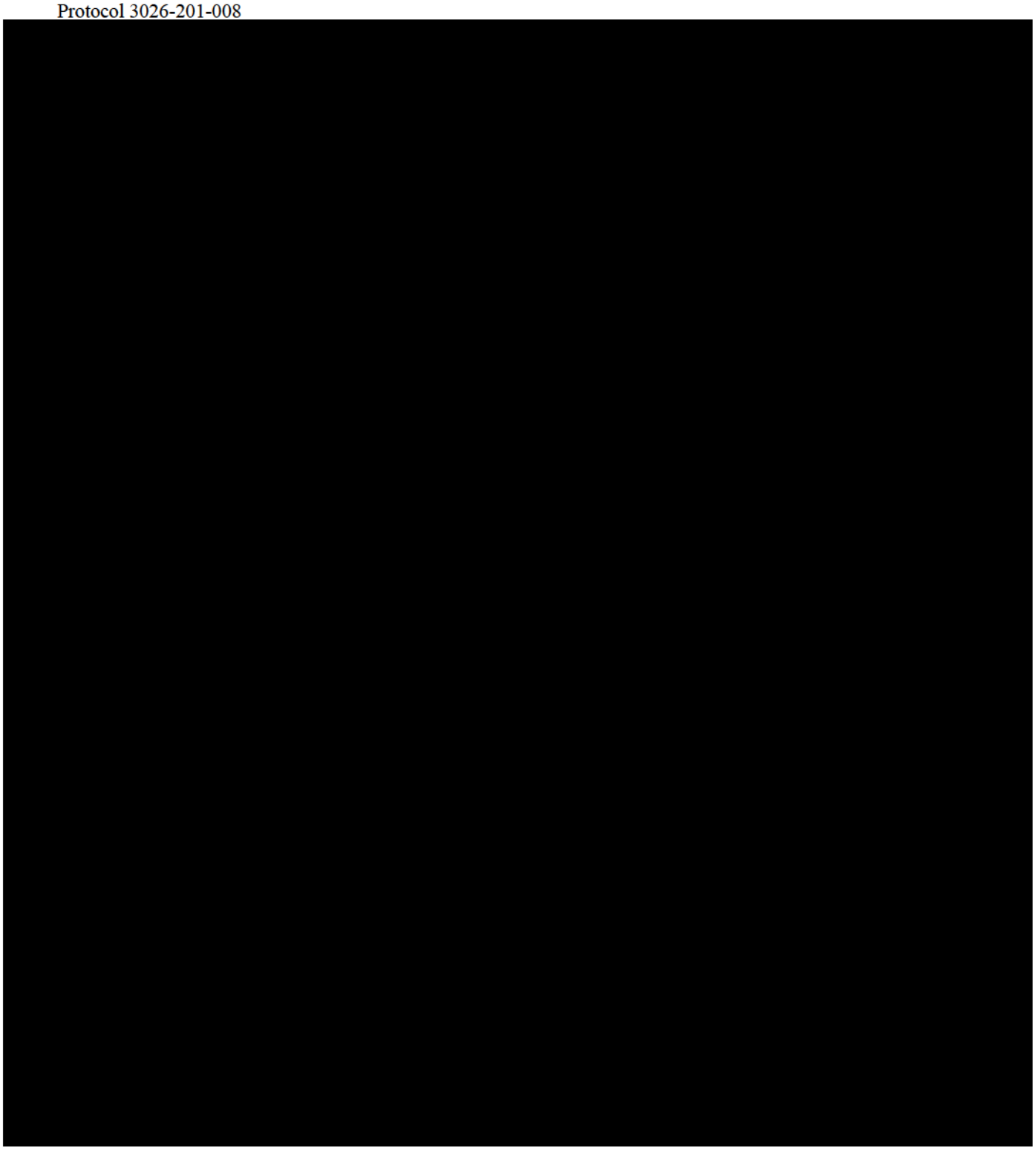

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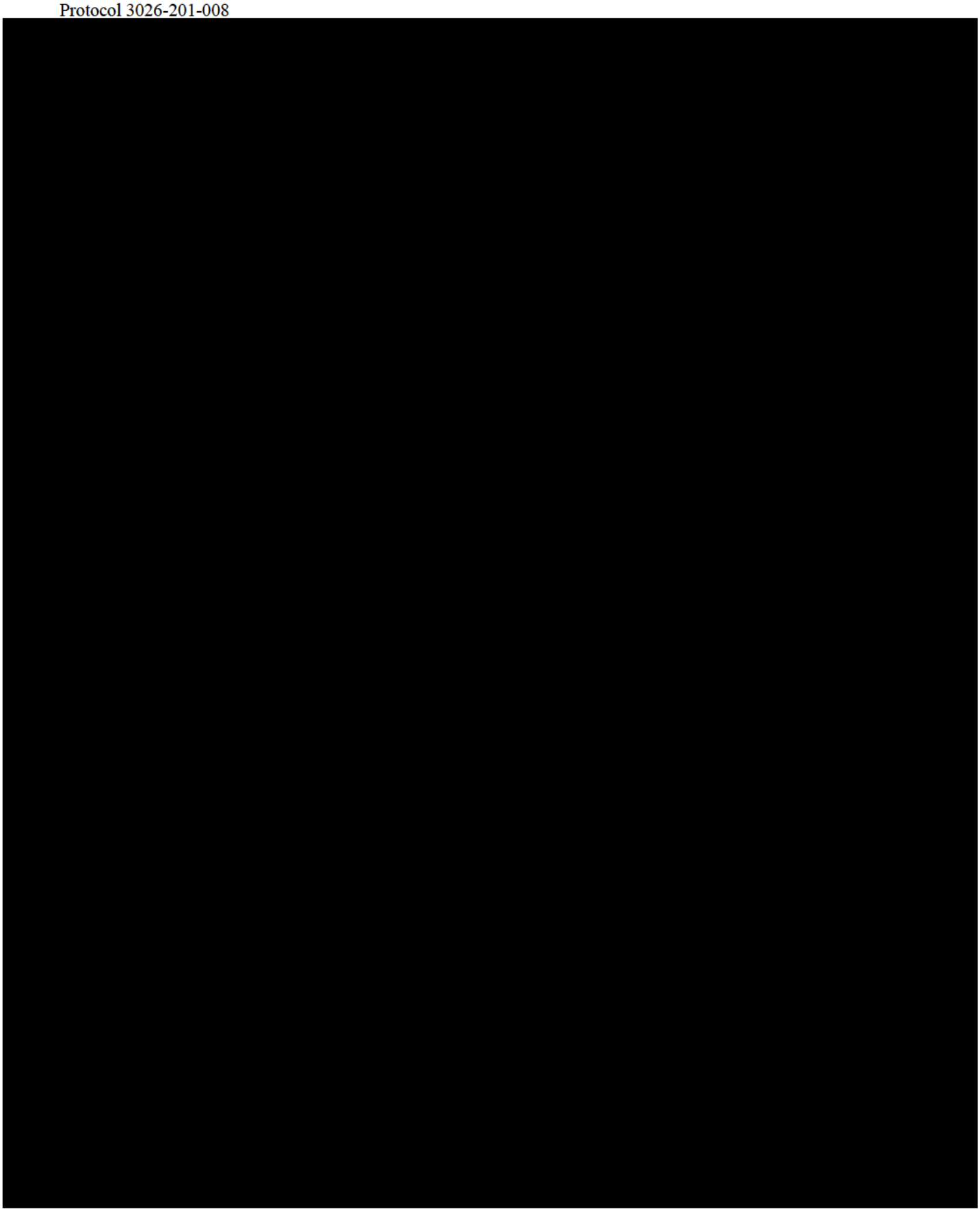

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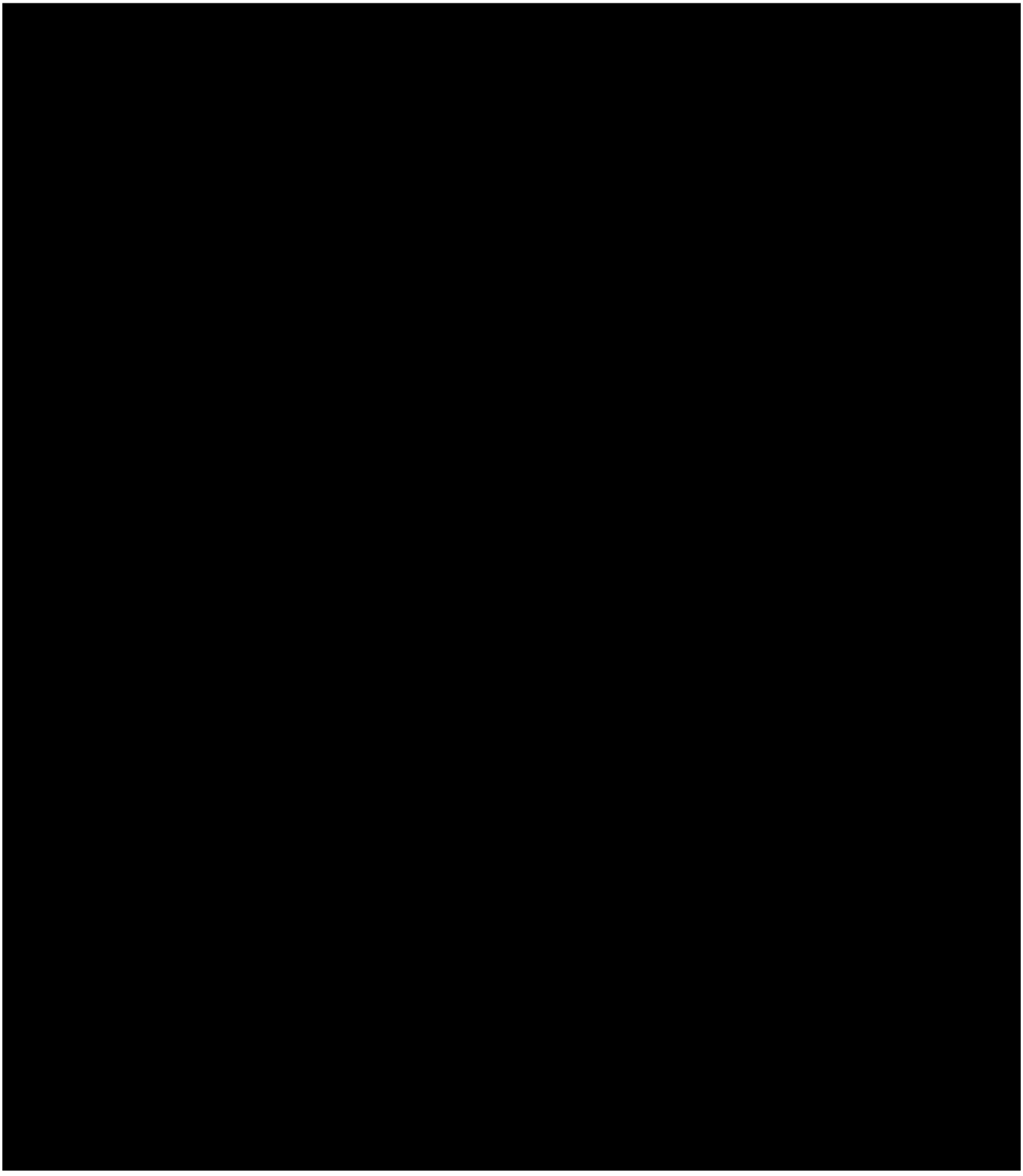

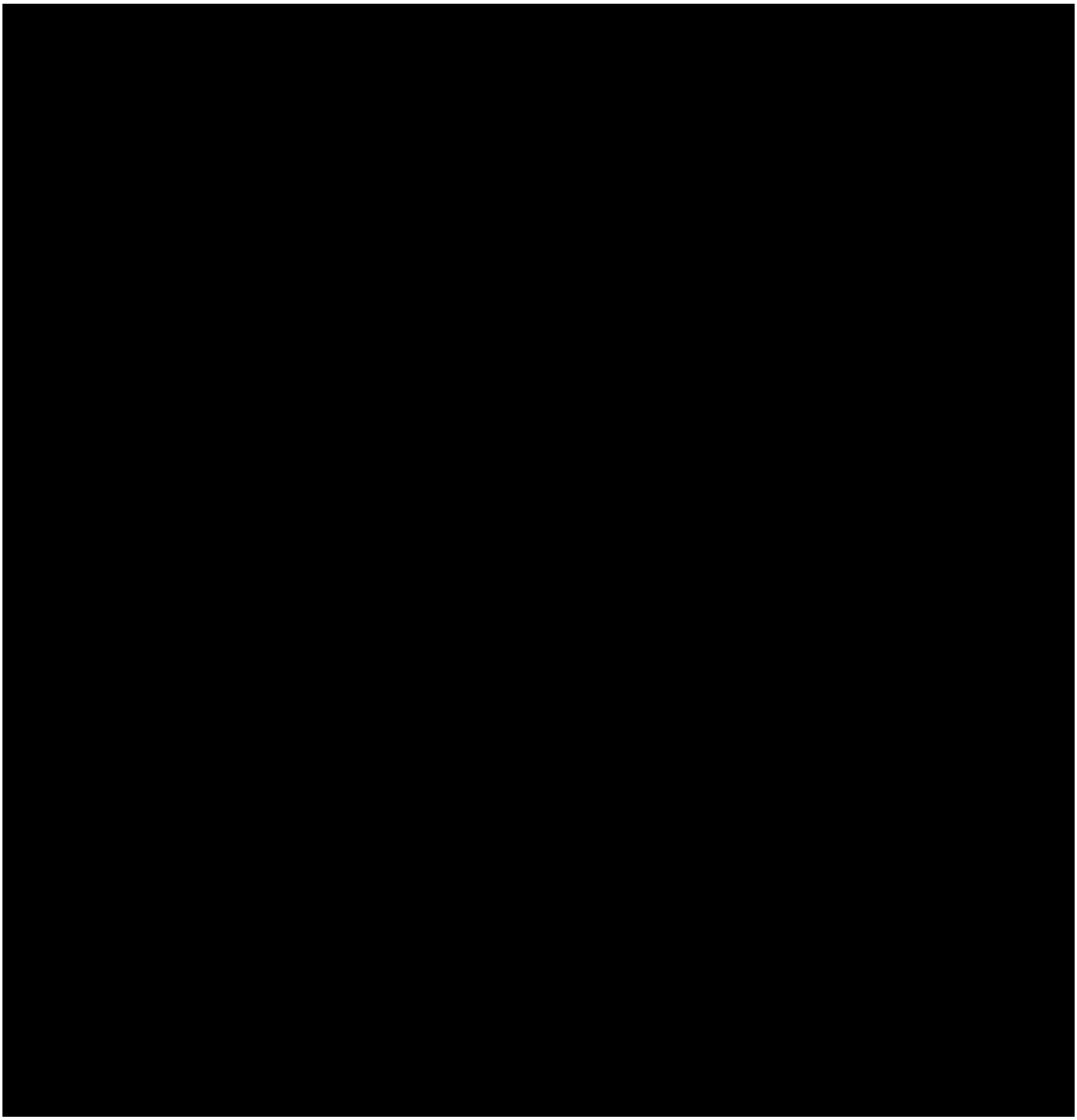

14.0 LITERATURE CITED

Andes D, Craig WA. In vivo pharmacodynamic activity of the glycopeptide dalbavancin. Antimicrob Agents Chemother. 2007;51(5):1633-42.

Calhoun J, Manring M, Shirtliff M. Osteomyelitis of the long bones. Semin Plast Surg. 2009;23(2):59-72.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404–13.

Dunne MW, Puttagunta S, Sprenger CR, Rubino C, Van Wart S, Baldassarre J. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. Antimicrob Agents Chemother. 2015;59(4):1849-55.

Evans SR, Rubin D, Follmann D, Pennello G, Huskins WC, Powers JH, et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). Clin Infect Dis. 2015;61(5):800–6.

Fritz J, McDonald J. Osteomyelitis: approach to diagnosis and treatment. Phys Sportsmed. 2008;36(1):nihpa116823.

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3):e18-55.

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 2016, Dec 19.