NCT03148756

Study ID: DAL-MD-09

Title: Phase 2, Open-Label, Randomized, Multicenter Study to Compare the Efficacy and Safety of Dalbavancin to Standard of Care Antibiotic Therapy for the Completion of Treatment of Patients with Complicated Bacteremia or Documented Infective Endocarditis

Protocol Date: 19 October 2016

1.0 TITLE PAGE

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Phase 2, Open-Label, Randomized, Multicenter Study to Compare the Efficacy and Safety of Dalbavancin to Standard of Care Antibiotic Therapy for the Completion of Treatment of Patients with Complicated Bacteremia or Documented Infective Endocarditis

DAL-MD-09

Dalbavancin

IND 060613 /EudraCT 2016-004170-17

Original Protocol Date: 19 October 2016

Confidentiality Statement

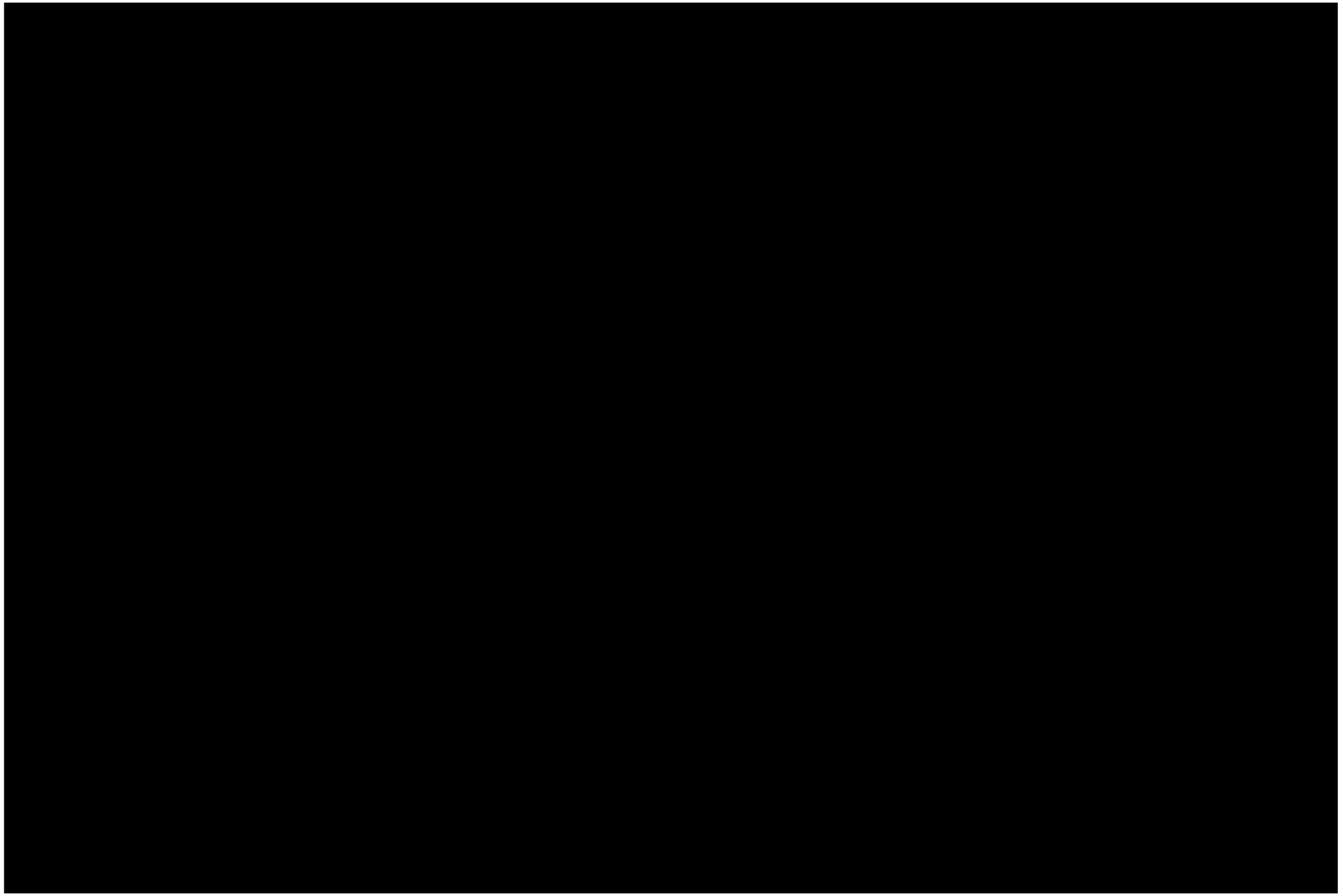
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

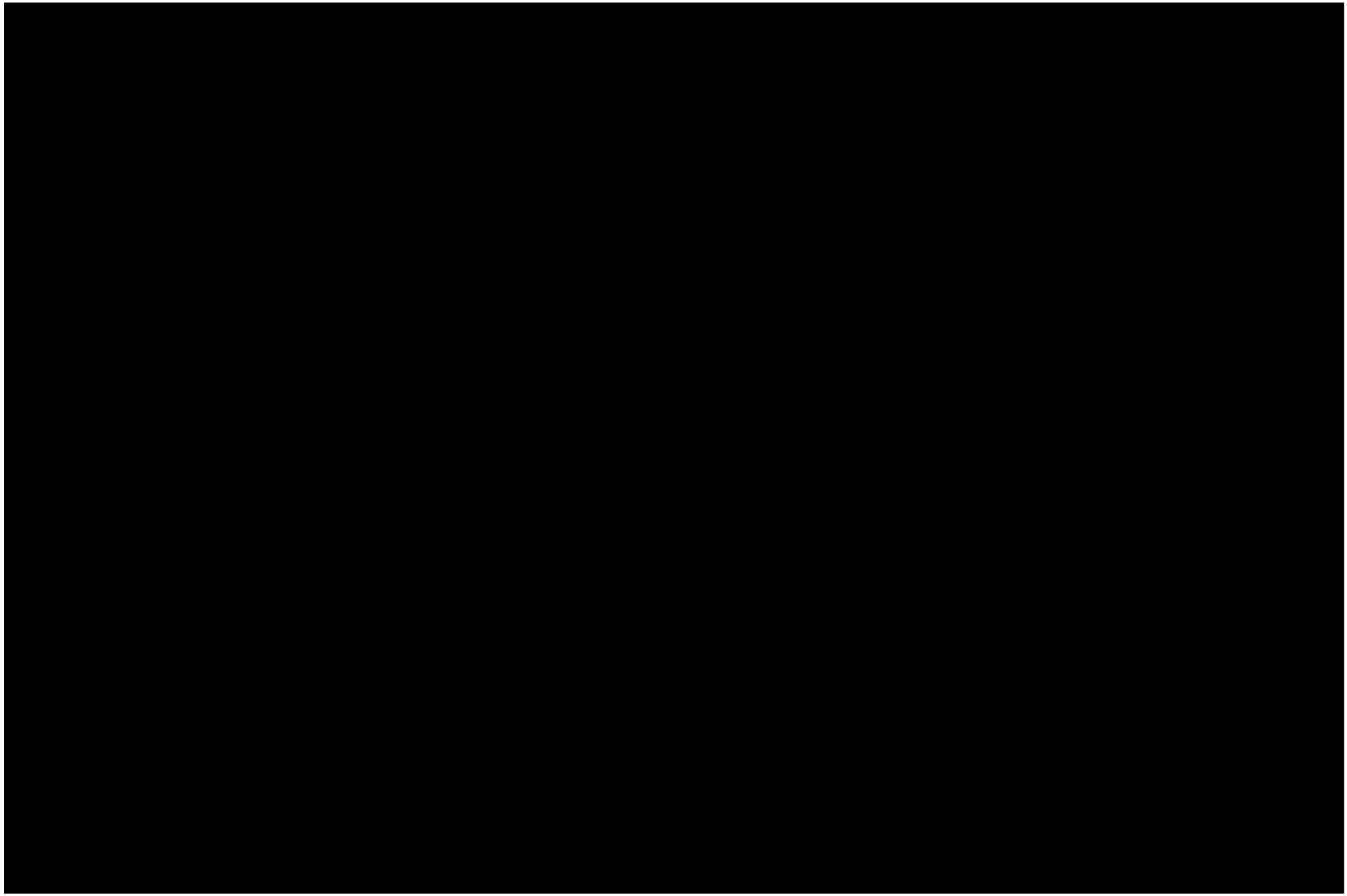
CLINICAL STUDY SYNOPSIS: Study DAL-MD-09	
Title of Study	Phase 2, open-label, randomized, multicenter study to compare the efficacy and safety of dalbavancin to standard of care antibiotic therapy for the completion of treatment of patients with complicated bacteremia or documented infective endocarditis
Study Centers (Country)	Approximately 90 study centers (global)
Development Phase	2
Objective	Primary: The primary objective of this study is to compare the clinical efficacy at Day 84 of dalbavancin to that of standard of care antibiotic therapy used to consolidate therapy for the treatment of patients with complicated bacteremia (signs or symptoms of metastatic foci of infection) OR documented infective endocarditis (IE) known to be caused by susceptible gram-positive organisms in the intent-to-treat (ITT) population. Secondary: • To compare clinical outcomes of dalbavancin with the standard of care antibiotic therapy at Day 42 in the ITT and clinically evaluable (CE) population • To compare mortality of dalbavancin with the standard of care antibiotic therapy at Day 84 after initiation of study drug therapy in the safety population • To compare clinical outcomes at Day 84 of dalbavancin with the standard of care antibiotic therapy in the CE population • To compare clinical outcomes by pathogen at Day 42 and Day 84 of dalbavancin with the standard of care antibiotic therapy in the ITT and CE populations • To compare microbiological outcomes by pathogen identified prior to study drug initiation at Day 42 and Day 84 of dalbavancin with the standard of care antibiotic therapy in the ITT and CE-populations • To compare the safety and tolerability of dalbavancin with that of the standard of care antibiotic therapy in the safety population [redacted]

	[redacted]
Methodology	Multicenter, randomized, open-label, assessor-blinded, noninferiority, active-controlled, parallel-group study
Number of Patients	150 planned with 2:1 randomization to dalbavancin or standard of care antibiotic therapy with stratification based on screening pathogen: methicillin-susceptible *Staphylococcus aureus* [MSSA], methicillin-resistant *S aureus* [MRSA], or streptococci
Diagnosis and Main Criteria for Inclusion	Male and female patients ≥ 18 years old, diagnosed with complicated bacteremia OR definite or possible IE utilizing modified Duke criteria and gram-positive bacteremia at Baseline (excluding enterococci and coagulase-negative staphylococci), treated with appropriate standard of care antibiotic therapy for at least 72 hours (maximum 10 days) and with subsequent clearance of bacteremia prior to randomization to study treatment
Test Product, Dosage, and Mode of Administration	Dalbavancin 1500 mg intravenously (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 arm: 2 doses of dalbavancin: first dose on Day 1 and the second dose on Day 8 Comparator arm: 4 to 6 weeks of standard of care antibiotic therapy
Reference Therapy, Dosage, and Mode of Administration	Standard of care antibiotic for 4 to 6 weeks, based on baseline pathogen: **MSSA**: nafcillin (2 g IV q4h × 4-6 weeks) OR cefazolin (2 g IV q8h × 4-6 weeks), based on anatomy **MRSA**: vancomycin (15 mg/kg IV q12h × 6 weeks) OR daptomycin (8-10 mg/kg IV daily × 6 weeks) based on anatomy **Streptococci**: penicillin G (2-4 million units IV q4h × 4 weeks) plus (optional gentamicin 3 mg/kg IV or IM q24h x 2 weeks for relatively penicillin-resistant strains) OR ceftriaxone (2 g IV daily × 4 weeks) depending on minimum inhibitory concentration (MIC) and anatomy OR vancomycin (15 mg/kg IV q12h × 4 weeks) for penicillin-allergic patients Patients with impaired renal function will have their dosage of standard of care antibiotic treatment adjusted as needed, based on local standard of care.
Criteria for Evaluation	Clinical and microbiologic response

Primary Outcome Measures	The primary efficacy outcome measure is clinical response at Day 84 (± 7 days) in ITT population. Clinical response can be either success or failure. A patient will be defined as a clinical success if there is: • Resolution of clinical signs and symptoms of complicated bacteremia or IE such that no additional antibiotic therapy is required for the treatment of the complicated bacteremia or IE A patient will be defined as a clinical failure if any of the following criteria are met: • Ongoing signs and symptoms considered by the investigator to be related to complicated bacteremia or IE requiring additional antibacterial therapy or unplanned valve replacement • Recurrent bacteremia • Death during the study period up to the Visit 6 (Day 84) • Discontinuation of the study medication due to an adverse event (AE) A blinded adjudication committee will be used to review the data from each patient to establish the baseline diagnosis, final diagnosis, and final outcome, including reasons for treatment failure. Batched data from completed patients will be reviewed during the study in accordance with patient accrual rates. The primary efficacy analysis will be based on the adjudicated data.
Secondary Outcome Measures	1. Clinical outcome at Day 42 (end of treatment) in the ITT and CE populations 2. Day 84 mortality in the safety population 3. Clinical outcome at Day 84 in the CE population 4. Clinical outcome by pathogen at Day 42 and Day 84 in the ITT and CE populations 5. Microbiologic outcome by pathogen at Day 42 and Day 84 in the ITT and CE populations
[redacted]	[redacted]
Pharmacokinetic Analysis	Dalbavancin plasma pharmacokinetic (PK) sampling on Day 1, Day 8, Day 22, and Day 42. In addition, patients who receive dalbavancin who subsequently undergo valve surgery may have the option to have dalbavancin levels assessed in the resected valve tissue.

Statistical Methods	For the primary efficacy endpoint, the number and percentage of patients with outcomes of success and failure in the ITT population will be determined in each treatment group. The noninferiority hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance with a noninferiority margin of 10%. The observed difference in percentage of successes at Day 84 (dalbavancin group minus the standard of care antibiotic therapy group) will be determined and a 95% CI for the observed difference will be computed using the method proposed by Miettinen and Nurminen (Miettinen 1985), which corresponds to the p-value approach of the Farrington-Manning test (Farrington 1990). If the lower limit of the 95% CI for the difference in improvement rates in the ITT population is greater than -10%, the noninferiority of dalbavancin to standard of care antibiotic therapy will be concluded. Missing data for the primary outcome measure will be imputed as failure for the primary efficacy analysis. For all efficacy analyses, the baseline is defined as Day 1 before dosing. For secondary efficacy endpoints, 2-sided 95% CIs for the treatment difference between 2 groups will be provided using the method proposed by Miettinen and Nurminen (Miettinen 1985). Descriptive statistics, including number and percentage for the categorical variables, will be provided by treatment group. [redacted] No formal interim analyses will be performed. However, ongoing review and summary of patient safety will be performed to allow for early detection of a safety signal that may result from an AE or lack of efficacy of study drug. There will be no action to terminate the study early, unless there is a safety concern.
Sample Size Consideration	Assuming a point estimate for the primary outcome measure of clinical success rate of 90% in the dalbavancin treatment group and 83% in the standard of care treatment group, a noninferiority margin of 10%, a 1-sided Type I error of 0.025, and power of approximately 85%, a total sample size of 150 patients is required with 2:1 randomization ratio (100 patients in dalbavancin treatment group and 50 patients in standard of care treatment group). The randomization will be stratified based on screening pathogen: MSSA, MRSA, or streptococci.





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4.0 LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infections
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
CE	clinically evaluable
CFR	Code of Federal Regulations
Cr	creatinine
CrCl	creatinine clearance
DHHS	Department of Health and Human Services
[redacted]	[redacted]
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life

ICF	informed consent form
ICH	International Council on Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use
IDSA	Infectious Disease Society of America
IE	infective endocarditis
IEC	independent ethics committee
IND	Investigational New Drug (application)
IRB	institutional review board
ITT	intent to treat
IV	intravenous
IWRS	interactive web response system
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
PCS	potentially clinically significant
PD	pharmacodynamic
PICC	peripherally-inserted central catheter
PID	patient identification
PK	pharmacokinetic
RSM	regional site manager
SAE	serious adverse event
SF-12	Short Form-12
SOP	standard operating procedure
spp	species

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States
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 (DHHS) 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.

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

5.2 ETHICAL CONDUCT OF THE STUDY

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

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

5.3 PATIENT INFORMATION AND INFORMED CONSENT

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA authorization (in compliance with 21 CFR, Parts 50 and 312) or other appropriate documentation, according to local regulatory requirements, before participating in any study-related procedures.

Each patient will read, assent to an understanding of, and sign an instrument of informed consent or other locally applicable regulations and authorization form after having had an opportunity to discuss them 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 1 of this protocol. Signed copies of the ICF and the HIPAA or other locally applicable form 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 90 study centers.

The investigator is responsible for ensuring that an investigation 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 at each site must meet their 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 at each site 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

Infective endocarditis (IE), an infection affecting the cardiac valves or the endocardium, is a relatively rare disease, with an estimated annual incidence ranging from 3 to 7 per 100,000 person-years and a male:female case ratio greater than 2:1 (Correa de Sa 2010, Duval 2012, Federspiel 2012, Hoen 2013). However, IE is the third or fourth most common life-threatening infection syndrome (Baddour 2015). Approximately 90% of the cases of IE are associated with positive blood cultures, with staphylococci and streptococci as the predominant causative organisms (80%). Further, MRSA accounted for 37.2% of *Staphylococcus aureus* IE in the United States according to a recent cohort study (Fowler 2005).

Even with major advances in both diagnostic and therapeutic procedures, IE still carries a poor prognosis and a high mortality (Habib 2009). If left untreated, IE is generally fatal. Currently, with antibiotic treatment in industrialized countries, in-hospital mortality ranges from 15% to 22% (Murdoch 2009, Sy 2010, Selton-Suty 2012) with the highest mortality (40%) reported in the subset of patients with prosthetic valvular infections caused by *S aureus* (Hoen 2013). In 2010, IE was associated with 1.58 million disability-adjusted life-years or years of healthy life lost as a result of death and nonfatal illness or impairment (Murray 2012).

Despite improvements in mortality, treatment of IE is complex and includes prolonged antibiotic therapy with or without surgical intervention. Patients with complicated bacteremia and a deep focus of infection also typically require prolonged IV antibiotic therapy for longer than 2 weeks. Completion of 4 to 6 weeks of intravenous (IV) antibiotics typically requires placement of a central IV catheter, prolonged hospitalization, home nursing care, and/or admission to a long-term care facility for the duration of treatment. Complications of prolonged IV therapy include peripherally-inserted central catheter (PICC)-line associated thrombosis and catheter-related bloodstream infection.

The most recent treatment guidelines published by the American Heart Association/Infectious Disease Society of America (AHA/IDSA) (Baddour 2015) generally recommend IV antibiotic therapy for 4 to 6 weeks for IE affecting native valves, depending on the causative pathogen, resistance profile, and the specific valve affected. The treatment algorithm for staphylococcal and streptococcal IE includes an initial period of therapy intended to rapidly eradicate bacteremia and decrease the risk of embolic events and metastatic infection. This is followed by a completion phase, in which prolonged antibiotic therapy is administered to sterilize valvular vegetations and endomyocardial abscesses, thus decreasing the risk of relapse.

Dalbavancin is a lipoglycopeptide being developed for the treatment of complicated bacteremia and IE known to be caused by gram-positive organisms. It interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is administered IV as a 30-minute infusion and is currently approved for acute bacterial skin and skin structure infection (ABSSSI) in the United States and European Union as a single dose (1500 mg) or as a 2-dose regimen (1000 mg IV on Day 1 followed by 500 mg IV on Day 8). The advantages of dalbavancin include its potent activity against the relevant gram-positive pathogens in IE, including resistant phenotypes (Table 7-1), with lower MICs than vancomycin for staphylococci and streptococci, and its low potential for development of resistance. There is no geographic variability in susceptibility of key pathogens to dalbavancin (Table 7-2). Furthermore, a 2-dose, once-weekly regimen of dalbavancin can provide systemic antibiotic coverage for 6 weeks, eliminating the need for indwelling IV access and daily antibiotic administration. Dalbavancin has a favorable safety profile, having been evaluated in over 2400 patients in 8 Phase 2/3 studies.

Table 7-1. Activity of Dalbavancin Against Gram-Positive Pathogens Collected in 2014 US Surveillance

		Dalbavancin MIC (µg/mL)			
Organism	N	Range	50%	90%	% Susceptible[a]
S aureus: all	1625	0.008 - 0.12	0.06	0.06	100
Methicillin-susceptible	875	0.008 - 0.12	0.06	0.06	100
Methicillin-resistant	750	0.008 - 0.12	0.06	0.06	100
Viridans group streptococci	220	≤ 0.002 - 0.12	0.015	0.03	100
Penicillin-nonsusceptible	46	0.004 - 0.06	0.015	0.03	100
S pyogenes	108	≤ 0.002 - 0.06	0.008	0.03	100
S dysgalactiae	75	≤ 0.004 - 0.12	0.015	0.03	100
E faecalis	151	0.02 - > 0.25	0.06	0.06	97.6

Bacterial pathogens frequently implicated as causative agents of IE include *S aureus* (including MRSA), *Streptococcus pyogenes,* viridans group streptococci, Group C and G streptococci, and *Enterococcus* spp.

IE = infective endocarditis; MRSA = methicillin-resistant *S aureus*; MIC = minimum inhibitory concentration

[a] Susceptible at ≤ 0.25 µg/mL

Source: Dalbavancin International (Two Continents) Surveillance Report for 2014, JMI Laboratories; Protocol 14-DUR-01, May 2015.

Table 7-2. Activity of Dalbavancin against Gram-Positive Pathogens Collected in 2014 EU Surveillance

Organism	N	Dalbavancin MIC (µg/mL) Range	50%	90%	% Susceptible[a]
S aureus: all	1625	0.004 - 0.12	0.06	0.06	100
Methicillin-susceptible	1209	0.015 - 0.12	0.06	0.06	100
Methicillin-resistant	416	0.004 - 0.12	0.03	0.06	100
Viridans group streptococci	213	≤ 0.002 - 0.12	0.015	0.03	100
Penicillin-nonsusceptible	57	≤ 0.002 - 0.06	0.015	0.03	100
S pyogenes	106	0.004 - 0.12	0.008	0.03	100
S dysgalactiae	94	≤ 0.002 - 0.12	0.015	0.03	100
E faecalis	305	0.03 - > 0.25	0.06	0.06	98.4

Bacterial pathogens frequently implicated as causative agents of IE include *S aureus* (including MRSA), *Streptococcus pyogenes,* viridans group streptococci, Group C and G streptococci, and *Enterococcus* spp.

IE = infective endocarditis; MRSA = methicillin-resistant *S aureus*; MIC = minimum inhibitory concentration

[a] Susceptible at ≤ 0.25 µg/mL

Source: Dalbavancin International (Two Continents) Surveillance Report for 2014, JMI Laboratories; Protocol 14-DUR-01, May 2015.

Dalbavancin has demonstrated efficacy in both rat and rabbit models of IE due to *S aureus* (Candiani 1999, Lefort 2004). In the rat model of staphylococcal endocarditis, dalbavancin was as effective as vancomycin and teicoplanin at reducing the bacterial load in the heart, but with a lower dose and less frequent dosing intervals when compared with the standard of care antibiotic therapy agents (Table 7-3).

Table 7-3. Efficacy of Dalbavancin in Experimental Endocarditis in Rats Against Methicillin and Teicoplanin-Resistant *Staphylococcus aureus* L1524

Agent (MIC, µg/mL)	Dose (mg/kg, Route, Frequency)	Number of Survivors/ Total Number	Number of Sterile Samples[a]	Mean ± SD Log_{10} CFU/g of Heart
None		0/12	0/12	9.7 ± 0.3
Dalbavancin (0.13)	10 IV QD[b]	11/11[c]	4/11[c]	3.7 ± 2.2[d]
Dalbavancin (0.13)	1.25 IV QD[b]	8/12[c]	0/12	6.8 ± 1.6[c]
Teicoplanin (0.5)	20 IV BID[b]	6/8[c]	0/8	6.1 ± 2.1[c]
Vancomycin (1)	100 IM BID	8/10[c]	2/10	4.1 ± 2.2[d]
Pretreatment[e]				7.3 ± 1.0

BID = twice daily; CFU = colony-forming units; IM = intramuscular; IV = intravenous; log_{10} CFU/g = heart bacterial load; MIC = minimum inhibitory concentration; QD = once daily; SD = standard deviation

[a] Detection limits were 1.90 to 2.19 log_{10} CFU/g of heart, depending on heart weights.

[b] The first IV treatment was doubled for loading.

[c] $p < 0.05$ compared with untreated controls

[d] $p < 0.05$ compared with dalbavancin 1.25 mg/kg or teicoplanin groups

[e] Determined in a separate group of 6 infected animals just before the first scheduled treatment

Source: Candiani 1999

In the rabbit model of endocarditis, dalbavancin given once daily (10 mg/kg for 4 days) or as a single dose of 40 mg/kg was effective against a strain of *S aureus* (strain Lim-2) with reduced susceptibility to the glycopeptides vancomycin and teicoplanin (Table 7-4).

Table 7-4. Results of Treatment with Dalbavancin in Rabbits with Experimental *Staphylococcus aureus* Endocarditis (*S aureus* strain Lim-2)

Regimen	Log_{10} CFU/g of Vegetation (Mean ± SD) (Number of Sterile/Treated Animals)
Controls	9.4 ± 1.1 (0/15)
Dalbavancin 10 mg/kg once a day IV, 4 days	5.5 ± 2.1[a] (1/10)
Dalbavancin 40 mg/kg IV, single dose	6.9 ± 2.1[a] (0/10)

CFU = colony-forming units; IV = intravenous; log_{10} CFU/g = heart bacterial load; SD = standard deviation

[a] $p < 0.01$ versus controls

Source: Lefort 2004

In 5 Phase 2/3 clinical studies that evaluated the efficacy and safety of dalbavancin administered as a single dose (1500 mg IV), or as a 2-dose regimen (1000 mg IV on Day 1, 500 mg IV on Day 8), there were a total of 39 patients with *S aureus* bacteremia who had follow-up blood cultures. All 39 patients (100%) who received dalbavancin, including 10 with a catheter-related bloodstream infection, had clearance of bacteremia relative to 19/20 (95%) patients treated with comparators (vancomycin or linezolid for 10 to14 days) (Allergan, Data on File; Raad 2005).

In addition to its robust in vitro activity, the extended half-life of dalbavancin would allow completion of a 4 to 6 week antibiotic course with two 30-minute infusions. Human pharmacokinetics in both healthy volunteers and patients indicate persistent, robust microbicidal plasma levels against the relevant pathogens for > 42 days with a dalbavancin 2-dose regimen of 1500 mg on Day 1 and on Day 8, administered over 30 minutes by IV infusion. Dalbavancin may thereby optimize adherence and ease administration, while reducing healthcare resource utilization, allowing the patient to return to normal activities sooner, and eliminating the need for drug level monitoring.

Pharmacokinetic-pharmacodynamic (PK-PD) modeling indicates that even at trough plasma levels at Day 42, the plasma free drug area under the concentration curve/minimum inhibitory concentration (AUC/MIC) ratios support target attainment of 90% or greater against *S aureus* and streptococci using the 2-log kill target. Therefore, based on expected target attainment and surveillance MICs, the proposed dosing regimen provides more than adequate exposure to cover the most common pathogens encountered in complicated bacteremia and IE. Additional information regarding dosing justification is provided in Section 9.4.4.

The safety profile of dalbavancin has been characterized for a total cumulative dose of 1500 mg, whether administered as a single dose or in split weekly doses (1000 mg on Day 1 followed by 500 mg on Day 8). Adverse reactions have been evaluated for 2473 patients treated with dalbavancin: 1778 patients were treated with dalbavancin in 7 Phase 2/3 studies comparing dalbavancin with comparator antibacterial drugs and 695 patients were treated with dalbavancin in one Phase 3 study comparing dalbavancin single and 2-dose regimens (split weekly doses). Overall, the most common adverse reactions in patients treated with dalbavancin were nausea (4.7%), headache (3.8%), and diarrhea (3.4%). The median duration of adverse reactions was 3 days for patients receiving dalbavancin and 4 days for patients receiving comparator.

The safety database for the 3000-mg total dose includes 12 subjects from a Phase 1 study: 6 received a total of 3500 mg dalbavancin over 6 weeks (with a total of 2 mild adverse events [AEs]), and 6 received a total of 4500 mg dalbavancin over 8 weeks (with a total of 4 mild AEs and 1 moderate AE). No serious AEs were reported, and no subjects were discontinued or withdrew due to a treatment-emergent AE (Dunne 2015).

In summary, dalbavancin provides excellent coverage against the relevant gram-positive pathogens in complicated bacteremia or IE including either methicillin-susceptible *S aureus* (MSSA), methicillin-resistant *S aureus* (MRSA), and alpha- and beta-hemolytic streptococci, with demonstrated efficacy in preclinical models, and safety in over 20 clinical studies, including 8 Phase 2/3 studies. Further, the extended half-life of dalbavancin would allow completion of a 4 to 6 week antibiotic course with two 30-minute infusions (1500 mg on Day 1 and 1500 mg on Day 8), without the requirement of daily administration of IV antibiotics or a PICC line, its associated complications, and home nursing care.

Further information is found in the Dalbavancin Investigator's Brochure.

8.0 STUDY OBJECTIVES

Primary:

The primary objective of this study is to compare the clinical efficacy at Day 84 of dalbavancin with that of standard of care antibiotic therapy used to consolidate therapy for the treatment of patients with complicated bacteremia (signs or symptoms of metastatic foci of infection) or documented IE known to be caused by susceptible gram-positive organisms in the intent-to-treat (ITT) population.

Secondary:

- To compare clinical outcomes of dalbavancin with the standard of care antibiotic therapy at Day 42 in the ITT and clinically evaluable (CE) population
- To compare mortality of dalbavancin with the standard of care antibiotic therapy at Day 84 after initiation of study drug therapy in the safety population
- To compare clinical outcomes at Day 84 of dalbavancin with the standard of care antibiotic therapy in the CE population
- To compare clinical outcomes by pathogen at Day 42 and Day 84 of dalbavancin with the standard of care antibiotic therapy in the ITT and CE populations
- To compare microbiological outcomes by pathogen identified prior to study drug initiation at Day 42 and Day 84 of dalbavancin with the standard of care antibiotic therapy in the ITT and CE populations
- To compare the safety and tolerability of dalbavancin with that of the standard of care antibiotic therapy in the safety population

[redacted]

[redacted]

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This clinical study will be a Phase 2, multicenter, randomized, open-label, assessor-blinded, noninferiority, active-controlled, parallel-group study. The study will compare dalbavancin to standard of care antibiotic therapy for the completion of therapy in patients with complicated bacteremia or native valve IE caused by susceptible gram-positive organisms who have cleared their baseline bacteremia (Figure 9-1).

Eligible patients are those who have been diagnosed with complicated bacteremia or IE due to staphylococci or streptococci (excluding *Enterococcus* spp), have been treated with appropriate empiric/targeted antibiotic therapy, and in whom the blood cultures have become negative after at least 72 hours of initial antibiotic therapy (maximum 10 days).

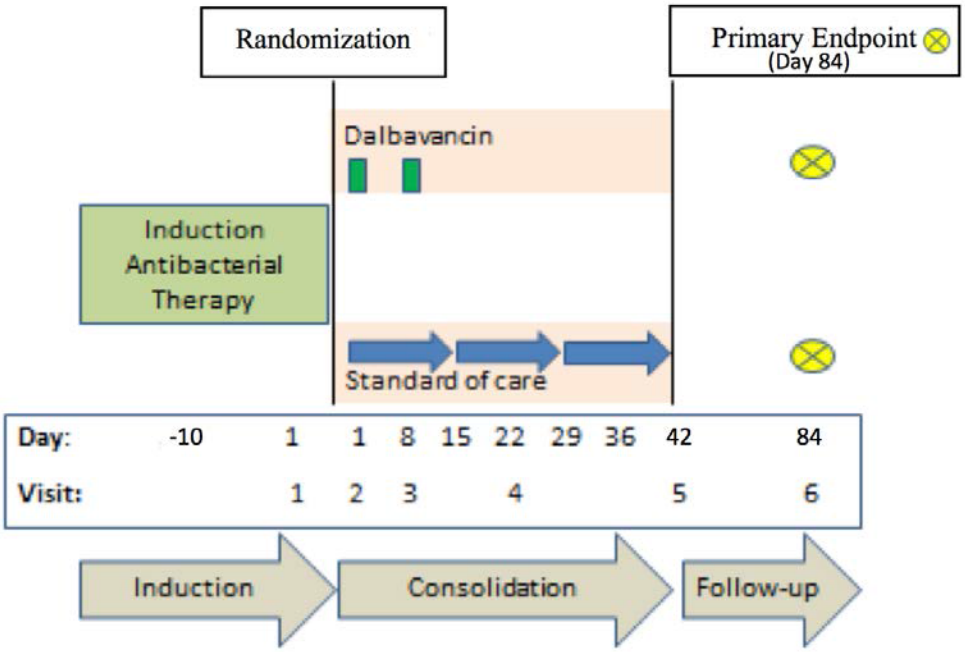
Patients with uncomplicated bacteremia due to *S aureus* will be excluded, and are defined as those with positive blood culture results and all of the following: exclusion of endocarditis by echocardiography; catheter-associated bacteremia and removal of catheter; no implanted prostheses; follow-up blood cultures drawn within 48 hours after initial set that do not grow screening pathogen and all follow-up blood cultures thereafter that do not grow the screening pathogen; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection (Liu 2011, Corey 2009). Patients with complicated bacteremia due to *S aureus* are defined as those with positive blood culture results who do not meet criteria for uncomplicated bacteremia

Patients will be randomized in a 2:1 scheme to receive either dalbavancin or a standard of care antibiotic regimen based upon the identification and antibiotic susceptibility pattern of the baseline organism. Those randomized to the dalbavancin treatment group will receive 2 doses of dalbavancin IV 1 week apart (1500-mg dose on Day 1 and Day 8 after randomization). Those patients randomized to the standard of care antibiotic therapy treatment group will receive an antibiotic regimen considered to be standard of care per the AHA/IDSA treatment guidelines based on the antibiotic susceptibility pattern of the pathogen isolated at Baseline for a duration of 4 to 6 weeks. If indicated, valve replacement surgery should be performed for patients enrolled in either treatment group.

Approximately 150 patients will be randomized using a 2:1 randomization scheme: 100 patients in the dalbavancin treatment group and 50 patients in the standard of care antibiotic therapy treatment group.

The figure below provides a schematic of the study design. The Schedule of Evaluations is presented in Section 2.0. Detailed descriptions of each study visit can be found in Section 9.5.5.

Figure 9-1. Study Design



Note: Induction Antibacterial Therapy: minimum 72 hours, maximum 10 days

For studies conducted at US (Investigational New Drug (application) [IND]) sites and non-US (non-IND) sites, data from IND and non-IND study sites will be pooled together for analysis.

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

The current standard of care for the antibiotic treatment of complicated bacteremia or IE uses a step-wise approach. The initial phase of treatment involves the initiation of empirical antibiotic therapy, definitive diagnosis (as per the modified Duke criteria), and the assessment of the need for early valve replacement, if applicable. Subsequent identification of the causative pathogen, including antibiotic susceptibility and MICs supports the choice of definitive antibiotic therapy and determination of the required duration of antibiotic treatment. Guidelines for the use of outpatient parenteral antibiotic therapy in the treatment of complicated bacteremia or IE similarly advocate that antibiotic therapy can be divided into an initial phase during which life-threatening complications of complicated bacteremia or IE are likely to occur (approximately 14 days) and a completion phase of therapy (2 weeks to 4-6 weeks) (Andrews 2001).

The proposed clinical study design of dalbavancin in the treatment of complicated bacteremia or IE is consistent with this standard of care. Specifically, patients will receive empirical antibiotic therapy pending a definitive diagnosis of complicated bacteremia or IE, identification of the causative pathogen, and the resolution of bacteremia. Patients will then be randomized into the study to complete their antibiotic therapy with either a 2-dose regimen of dalbavancin or the current standard of care with daily IV administration of antibiotic therapy for a total duration of 4 to 6 weeks (Baddour 2015).

While allowing antecedent antibiotic therapy prior to study enrollment may complicate the interpretation of the clinical and microbiological outcomes, the proposed clinical study design offers a number of advantages. First, it will support enrollment of patients with a confirmed diagnosis of complicated bacteremia or IE. Second, the proposed study design reflects the likely pattern of "real-world" dalbavancin use by clinicians for the completion of systemic antibiotic therapy for complicated bacteremia or IE without the need for in-dwelling IV access to support daily therapy. This takes full advantage of the unusual PK profile of dalbavancin and the introduction of this therapy into clinical practice would have a major impact on patient well-being and quality of life. Third, adequate treatment of complicated bacteremia or IE requires prolonged systemic antibiotic therapy to prevent relapse. Introduction of the 2-dose dalbavancin regimen should decrease the risk of relapse due to inadequate compliance with prolonged and complex antibiotic treatment. Finally, the proposed design of this clinical study is consistent with antibiotic stewardship principles, reserving dalbavancin therapy for patients with fully characterized infections and pathogens.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

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

1. Male or female patients ≥ 18 years old

2. A diagnosis of complicated bacteremia (signs or symptoms of metastatic foci of infection) OR IE based on modified Duke criteria, as below:

   Duke criteria include a **definite** diagnosis (presence of 2 major, 1 major and 3 minor, or 5 minor criteria) OR a **possible** diagnosis (1 major criterion and 1 minor criterion, or 3 minor criteria) as stated below:

   a. Major clinical criteria:

      i. Blood cultures positive for IE:

         1) Gram-positive microorganisms typically associated with IE (eg, *S viridans, S bovis, S aureus* in the absence of a primary focus) identified from 2 separate blood cultures

         2) Microorganisms consistent with IE identified from persistently positive blood cultures (at least 2 positive cultures of blood samples drawn > 12 hours apart, or positive results of all 3 or a majority of 4 or more separate blood cultures [with first and last samples drawn at least 1 hour apart])

      ii. Evidence of endocardial involvement:

         1) Echocardiogram positive for IE with pendulum-like intracardiac mass on valve or supporting structures, or in the path of regurgitant jets

         2) New valvular regurgitation (worsening or changing of pre-existing murmur not a sufficient criterion) when confirmed by echocardiogram

   b. Minor clinical criteria:

      i. Predisposition to IE, such as predisposing heart condition, or IV drug use

      ii. Fever, defined as a temperature > 38°C

iii. Vascular phenomena, such as conjunctival hemorrhage, and Janeway's lesions

iv. Immunologic phenomena, such as glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

v. Microbiologic evidence: positive blood cultures but with no major clinical criterion met or serologic evidence of active infection with an organism consistent with IE

3. Gram-positive bacteremia at Screening (excluding enterococci) defined as any of the following: MSSA, MRSA, or streptococci

4. Treated with appropriate standard of care antibiotic therapy for at least 72 hours (maximum 10 days)

5. Subsequent defervescence for at least 24 hours and clearance of bacteremia from the qualifying pathogen (at Screening), with negative blood culture incubated for at least 72 hours (5 days for slow-growing fastidious gram-positive organisms)

6. 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 out-patient procedures as required by the protocol and the antibiotic treatment administered.

7. Patients must be expected to survive with appropriate antibiotic therapy and appropriate supportive care throughout the study.

8. Written informed consent obtained from the patient before the initiation of any study-specific procedures

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 study medication

2. Embolic events, including cerebrovascular ischemic or hemorrhagic stroke

3. History of prosthetic valve surgery, cardiac device (eg, implantable cardioverter-defibrillator [ICD], permanent pacemaker, cardiac valve support ring), or prosthetic joint

4. Known or suspected left-sided endocarditis due to *S aureus*, large mobile vegetations (> 10 mm) on mitral valves, or presence of perivalvular abscess

5. Uncomplicated bacteremia due to S aureus, defined as positive blood culture results and all of the following: exclusion of endocarditis by echocardiography; catheter-associated bacteremia and removal of catheter; no implanted prostheses; follow-up blood cultures drawn within 48 hours after initial set that do not grow screening pathogen and all follow-up blood cultures thereafter that do not grow the screening pathogen; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection

6. Gram-negative bacteria or fungi isolated from blood cultures

   Note: If a gram-negative bacteremia or fungemia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the gram-negative bacteremia or fungemia.

7. Presence of heart failure associated with diagnosis of IE (left ventricular ejection fraction < 40%)

8. Presence of intravascular material (excluding cardiac stents) or removable infection source not intended to be removed within 4 calendar days postrandomization

9. Planned valve replacement surgery in the first 3 days following randomization

10. Refractory shock, significant hepatic insufficiency or severe leukopenia (absolute neutrophil count [ANC] < 500 cells/mm^3)

11. Patients with known osteomyelitis

12. History of hypersensitivity reaction to dalbavancin or other drugs of the glycopeptide class of antibiotics

13. Infection with enterococci, coagulase-negative staphylococci, or with an organism not susceptible to dalbavancin (dalbavancin mean inhibitory concentration [MIC] > 0.25 µg/mL) or vancomycin (vancomycin MIC > 2 µg/mL)

14. Immunosuppression/immune deficiency, including hematologic malignancy, recent bone marrow transplant (in posttransplant hospital stay), ANC < 500 cells/mm^3, or receiving immunosuppressant drugs after organ transplantation, or oral steroids (> 20 mg prednisolone per day or equivalent), chronic granulomatous disease, and known or suspected HIV infection with a CD4 cell count < 200 cells/mm^3 or with a past or current AIDS-defining condition and unknown CD4 count

15. Concomitant systemic antibacterial therapy for gram-positive infections (postrandomization), other than that allowed in the protocol

16. Concomitant condition requiring any antibiotic therapy (postrandomization) that would interfere with the assessment of study therapy for the condition under study

17. Pregnant or nursing females; positive urine (or serum) pregnancy test at Screening. 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 of 5, 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 (IUD)

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

    e) Partner vasectomy at least 6 months prior to Baseline

18. 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

19. Unwilling or unable to follow study procedures

20. Employee or immediate relative of an employee of the sponsor, any of its affiliates or partners, or the study center

9.3.3 Removal of Patients from Therapy or 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 will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, 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: Patients can be prematurely discontinued from study therapy after careful consideration for 1 of the following reasons and may 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)
- Occurrence of an AE that, in the opinion of the investigator, warrants the patient's permanent discontinuation from IV study drug
- Known pregnancy or breastfeeding during the study therapy administration period. A female patient whose pregnancy test is positive at Day 28 or 42 must be followed through the immediate postnatal period or until termination of the pregnancy. Study center personnel must report every pregnancy as soon as possible (within 24 hours of learning of the pregnancy; as described in Section 9.5.2.8).
- The patient meets criteria for drug-induced liver injury per Section 9.5.2.9, at the discretion of the investigator
- Patient is noncompliant with study drug.
- Patient has an insufficient therapeutic response to study drug (ie, lack of efficacy). A patient who does not show signs of improvement despite treatment with study drug for an appropriate length of time or a patient who shows signs of clinical worsening at any time may be prematurely discontinued from study therapy.
- If a gram-negative bacteremia or fungemia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the gram-negative bacteremia or fungemia.
- Investigator determines that it is in the best interest of the patient to discontinue study drug, due to reasons other than an AE
- 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
- Other

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 the Schedule of Evaluations. A clear description of reason for premature discontinuation from investigational product 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 electronic case report form (eCRF). Patients who discontinue from study therapy should continue to have follow-up safety visits.

9.3.3.2 Withdrawal From Study

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

- Screen failure (failure to meet inclusion/exclusion criteria) (before administration of first dose of study therapy)
- Withdrawal of consent (a clear reason must be documented)
- AE (before administration of first dose of study therapy)
- Protocol deviation/violation, including lack of compliance
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- Study or site prematurely terminated by sponsor for any reason

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

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

Assessments and Procedures: Patients may withdraw from the study, or be withdrawn at the request of the investigator or sponsor. A patient who is withdrawn from the study should be encouraged to undergo the assessments for premature discontinuation conducted as outlined in the Schedule of Evaluations on the day of withdrawal. All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at early termination (ET). A *final assessment* will be defined as completion of the evaluations scheduled for the Final Visit at the end of study (Day 84). 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

Patients in this study who prematurely discontinue treatment 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 dalbavancin 1500 mg IV over 30 (± 5) minutes on Day 1 and Day 8. Refer to Section 9.4.5 for dose adjustments for patients with chronic renal insufficiency.

9.4.1.2 Standard of Care Treatment Group

During the Induction Period, once the screening pathogen susceptibilities are known, investigators are encouraged to use one of the allowed standard of care antibiotics, per protocol. For patients randomized to standard of care antibiotic therapy, the counting of days for the duration of therapy may begin on the first day on which blood cultures are negative during the Induction Period, if standard of care antibiotic therapy is used per protocol, and if appropriate.

Patients randomized to the standard of care antibiotic therapy treatment group will receive the following antibiotic(s) for the specified duration based on baseline pathogen:

Baseline Pathogen	Standard of Care Therapy
MSSA[a]	nafcillin (2 g IV q4h × 4-6 weeks) OR cefazolin (2 g IV q8h × 4-6 weeks) based on anatomy
MRSA	vancomycin (15 mg/kg IV q12h × 6 weeks)[b] OR daptomycin (8-10 mg/kg IV daily × 6 weeks) based on anatomy
Streptococci	penicillin G (2-4 million units IV q4h × 4 weeks) plus (optional gentamicin[c] 3 mg/kg IV or IM q24h x 2 weeks for relatively penicillin-resistant strains) OR ceftriaxone (2 g IV daily × 4 weeks) depending on minimum inhibitory concentration (MIC) and anatomy OR vancomycin (15 mg/kg IV q12h × 4 weeks) for penicillin-allergic patients

IV = intravenous; qxh = every x hours; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*

[a] Vancomycin is also appropriate for patients with MSSA and anaphylactoid-type hypersensitivity to beta-lactams.

[b] Patients on vancomycin will have dose adjustment based on local standard of care to achieve serum trough concentrations of 10-15 µg/mL (for streptococci) or 10-20 µg/mL (for staphylococci).

[c] When used, it is preferred that gentamicin (3 mg/kg) be given as a single daily dose in adults with endocarditis caused by viridans group streptococci; as a second option, gentamicin can be administered daily in 3 equally divided doses. Gentamicin dose should be adjusted to achieve peak serum concentration of 3–4 µg/mL and trough serum concentration of < 1 µg/mL when 3 divided doses are used; there are no optimal drug concentrations for single daily dosing.

Patients with impaired renal function will have their dosage of standard of care antibiotic treatment adjusted as needed, based on local standard of care.

Any alteration in study drug therapy because of unusual clinical circumstances must be discussed with medical monitor in advance.

Refer to Section 9.4.8 for additional antibacterial therapy allowed during the study.

9.4.2 Identity of Investigational Product

Dalbavancin is supplied as a single-use vial of sterile, lyophilized preservative-free powder containing 500 mg of dalbavancin. Each vial should be reconstituted and further diluted prior to administration by addition of 5% dextrose [5% glucose] solution (D5W) in accordance with the study pharmacy manual. Each participating site 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 or designee will write the patient identification number, and date on the label.

With the exception of dalbavancin, all other study drugs will be commercially labeled and supplied by the study center, unless otherwise arranged by the Sponsor. All study drugs should be kept in a secure place under appropriate storage conditions, as specified on the drug labeling and package insert.

The investigator or designee is responsible for recording the receipt and use of all study drugs 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 at the Screening Visit, study personnel will register the patient in the interactive web randomization system (IWRS) system, the system will associate that patient with the next available treatment in the appropriate stratum on the randomization schedule, and the system will assign the patient a sequential patient identification (PID) number. Patients will be randomized to receive either a 2-dose regimen of dalbavancin or 4 to 6 weeks of standard of care antibiotic therapy in accordance with Section 9.4.1.2 in a 2:1 allocation ratio based on the IWRS-generated randomization schedule.

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

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 by IWRS at each dispensing visit (Day 1 and Day 8 for dalbavancin), and, if applicable, daily (by dose) for standard of care antibiotic therapy.

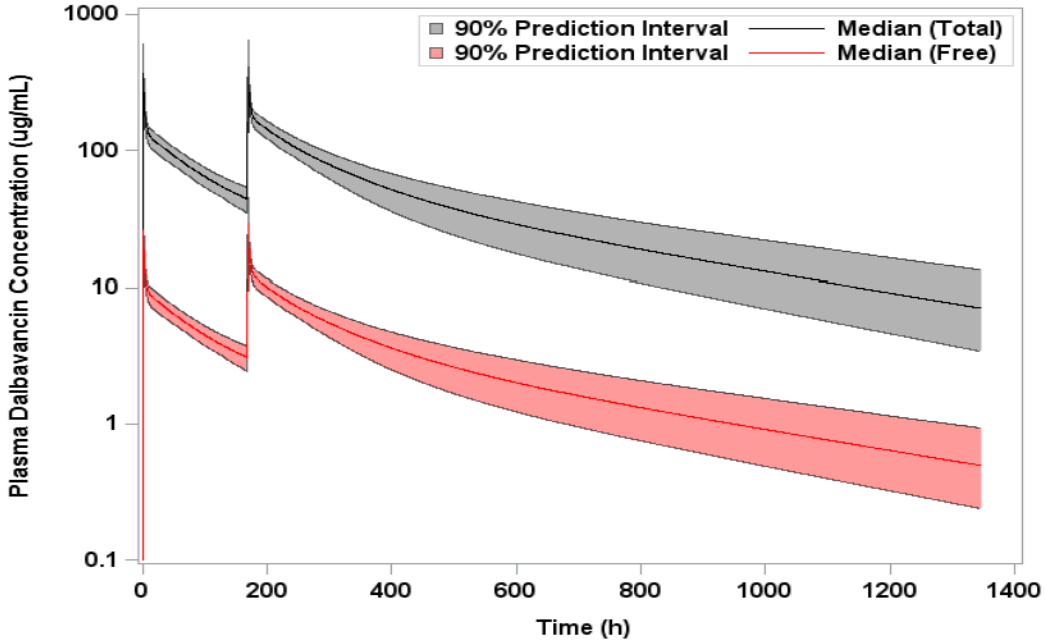
9.4.4 Selection of Dosages in the Study

The dalbavancin dosing regimen consists of 1500 mg on Day 1 and on Day 8, administered over 30 minutes by IV infusion. Based on a comparison to the updated nonclinical PK/PD target of fAUC/MIC (Lepak 2015), this regimen is expected to provide sufficient therapeutic concentrations of free drug against *S aureus* and other susceptible gram-positive pathogens through Day 42.

Consistent with prior nonclinical investigation (Andes 2007), Lepak et al (Lepak 2015) found fAUC/MIC to be the most relevant PK/PD index in a neutropenic murine thigh infection model, with mean free-drug daily AUC/MICs for net stasis, 1-log kill, and 2-log kill of 27.1, 53.3, and 111.1, respectively. To justify the proposed dosing regimen, a target attainment analysis was conducted using the updated population PK model (Study DAL-MS-01). In the PK simulation, the proposed regimen was simulated using the Bayesian post hoc estimates of each of the 703 patients in the merged Phase 2/3 population PK dataset. As with previous target attainment analyses, free drug levels were assumed to be 7% of total drug concentrations. As a conservative assumption, the mean daily AUC for target attainment was calculated based on dalbavancin levels on Day 42. For the MIC, the dalbavancin *S aureus* MIC_{90} of 0.06 mg/L was used. Results of this simulation analysis showed target attainments of > 99%, > 99%, and 90% for the net stasis, 1-log kill, and 2-log kill targets, respectively. For an even more conservative estimate, the US breakpoint for susceptibility of *S aureus* to dalbavancin of 0.25 mg/L was also used: the 90% target attainment was achieved through Day 42 (stasis), Day 36 (1-log kill), and Day 28 (2-log kill) after clearance of bacteremia.

Simulations designed to evaluate plasma concentration-time profiles suggest that a 2-dose regimen of dalbavancin of 1500 mg given on Days 1 and 8 will provide plasma concentrations above the MIC_{99} of *S aureus* for an average of 49 days after the start of therapy Figure 9-2.

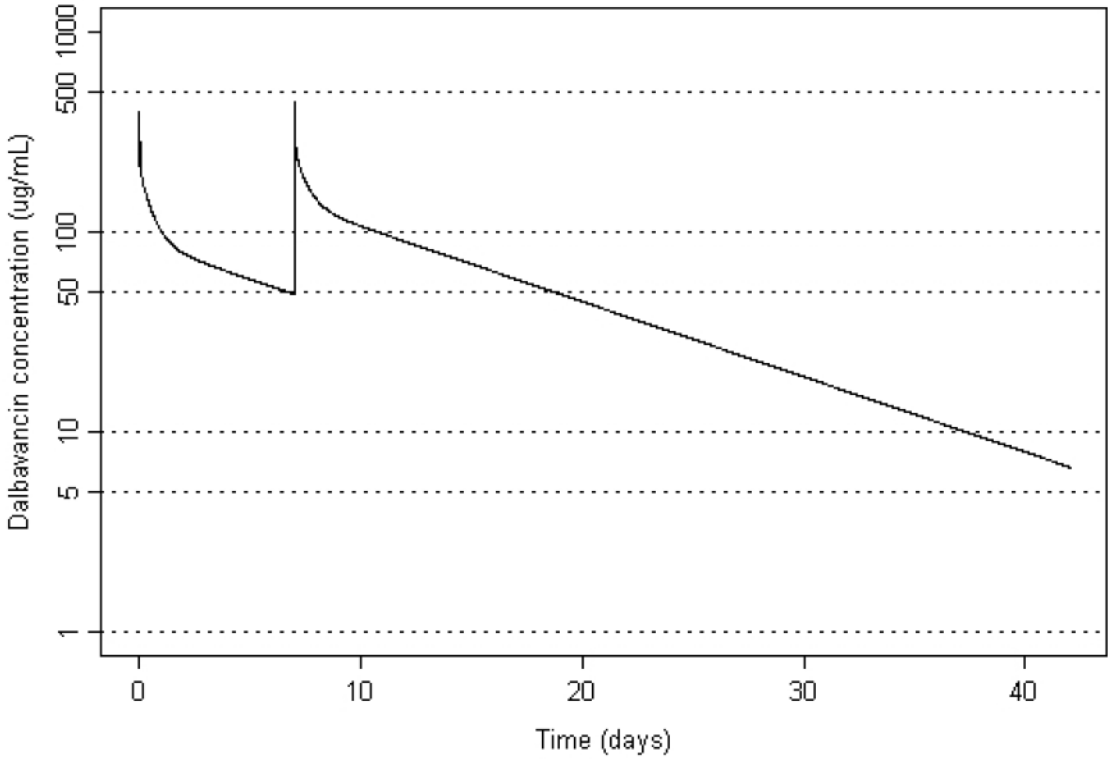
Figure 9-2. Simulated Mean Plasma PK Profile of Dalbavancin



Source: Allergan data on file

Figure 9-3 shows the time course of total dalbavancin concentration over the 6-week course of therapy for a typical patient. For this typical patient, Day 42 total drug concentration was 6.7 µg/mL [free drug = 7% × 6.7 = 0.47 µg/mL], which is greater than 7-fold the MIC_{90} value of 0.06 µg/mL for *S aureus*, and > 15-fold the MIC_{90} value of 0.03 µg/mL for beta-hemolytic streptococci (Dalbavancin International [Two Continents] Surveillance Report for 2014) even at the end of a 6-week course of therapy.

Figure 9-3. Dalbavancin Concentration Time Course for a Typical Subject under the Proposed Regimen



Source: Allergan data on file

9.4.5 Selection and Timing of Dose for Each Patient

For patients randomized to the dalbavancin treatment group, the dosage of dalbavancin administered will be determined based on individual estimated patient serum creatinine clearance (CrCl) levels as follows:

- Patients with CrCl ≥ 30 mL/min and patients receiving regular hemodialysis or peritoneal dialysis will receive 1500 mg IV dalbavancin over 30 (± 5) minutes on Day 1 and on Day 8.

- Patients with CrCl < 30 mL/min who are not receiving regular hemodialysis or peritoneal dialysis will receive 1000 mg IV dalbavancin over 30 (± 5) minutes on Day 1 and on Day 8.

Formulae for estimation of serum creatinine clearance are provided in Appendix 3.

Patients randomized to the standard of care antibiotic therapy treatment group will receive an antibiotic considered standard of care for 4 to 6 weeks according to Section 9.4.1.2 and results of antibiotic susceptibility testing for baseline pathogen. The standard of care antibiotic agents are to be prepared and administered according to instructions provided in the commercial label.

9.4.6 Blinding

This study will be conducted as an open-label, assessor-blinded investigation; no blinding of assigned treatment will occur at the study centers. A list of patient randomization codes will be generated by Statistical Programming and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

9.4.7 Unblinding

Not applicable

9.4.8 Prior and Concomitant Therapy

Medication history during the 30 days prior to ICF signing will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

Any medication taken by the patient, other than study drugs, is considered concomitant medication. All concomitant medications from Screening (Visit 1) through Day 42 ± 3 days (Visit 5) must be recorded in the patient's medical record and on the eCRFs. Between the Day 42 Visit and Day 84 Visit, all concomitant medications for an AE or any antibacterial therapy should be recorded in the patient's medical record and on the eCRF.

At each visit the investigator will obtain information on any therapeutic interventions (eg, drug and nondrug therapy, surgery) provided. The use of any other investigational drug is prohibited and patients may not participate in any other studies involving marketed products concomitantly while in this study.

The use of other (non-antibacterial) medications should be limited to those essential for the care of the patient. All medications required by the patient to manage underlying illnesses, other than infection under study, and any drugs that may be required for emergency treatments must be recorded on the :eCRF.

Concomitant treatment with an aminoglycoside will not be permitted, unless used as standard of care in the comparator arm.

Concomitant systemic antibacterials (other than dalbavancin or comparator study drug) are prohibited during the study, up to Day 84, with the following exceptions:

- Vancomycin oral 125 mg or 250 mg every 6 hours may be used in both treatment groups for the treatment of *Clostridium difficile* infections and may be continued as required throughout the duration of the study. The sponsor will not provide oral vancomycin.
- Metronidazole IV or oral 500 mg every 8 hours may be used in both treatment groups for the treatment of *C difficile* infections and may be continued as required throughout the duration of the study. The sponsor will not provide metronidazole.
- Other antibacterials that do not achieve therapeutic levels in the serum (eg, nitrofurantoin) may be considered. Consultation with the medical monitor is advised before use of these antibiotics.

9.4.9 Monitoring Treatment Compliance

Intravenous study therapy will be administered under the supervision of investigative site personnel, and infusion date, start, and stop time will be documented in the eCRF.

The investigator must maintain records documenting the receipt, use, loss, or other disposition of the investigational product(s). The sponsor may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities. At the end of the study, the sponsor will provide instructions as to disposition of any unused investigational product. If the sponsor authorizes destruction at the study center, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be documented.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy Assessments

9.5.1.1 Primary Efficacy Assessments

The primary efficacy outcome measure is clinical response at Day 84 in the ITT population.

Clinical response can be either **success** or **failure**. A patient will be defined as a clinical **success** if there is:

- Resolution of clinical signs and symptoms of complicated bacteremia or IE such that no additional antibiotic therapy is required for the treatment of complicated bacteremia or IE

A patient will be defined as a clinical **failure** if any of the following criteria are met:

- Ongoing signs and symptoms considered by the investigator to be related to complicated bacteremia or IE requiring additional antibacterial therapy or unplanned valve replacement
- Recurrent bacteremia
- Death during the study period up to the Visit 6 (Day 84)
- Discontinuation of the study medication due to an AE

The primary efficacy endpoint is accepted as a marker of clinical success in the treatment of complicated bacteremia or IE and has been used in other clinical studies (Fowler 2006). Day 84 was selected in this study as it occurs approximately 6 weeks after treatment completion, allowing time for detection of relapse.

A blinded adjudication committee will be used to review the data from each patient to establish the baseline diagnosis, final diagnosis, and final outcome, including reasons for treatment failure. Batched data from completed patients will be reviewed during the study in accordance with patient accrual rates. The primary efficacy analysis will be based on the adjudicated data.

9.5.1.2 Secondary Efficacy Assessments

The secondary efficacy assessments are as follows:

1. Clinical outcome at Day 42 (end of treatment) in the ITT and CE populations

   Clinical outcome can be either **Success** or **Failure**. A patient will be defined as a clinical **Success** if there is:

   - Resolution of clinical signs and symptoms of complicated bacteremia or IE such that no additional antibiotic therapy is required for the treatment of complicated bacteremia or IE.

   A patient will be defined as a clinical **Failure** if any of the following criteria are met:

   - Ongoing signs and symptoms considered by the investigator to be related to complicated bacteremia or IE requiring additional antibacterial therapy
   - Recurrent bacteremia
   - Death during the study period up to the Day 42 visit

2. Day 84 mortality in the safety population

3. Clinical outcome at Day 84 in the CE population

   Clinical outcome can be either **Success** or **Failure/Relapse.** A patient will be defined as a clinical **Success** if there is:

   - Resolution of clinical signs and symptoms of complicated bacteremia or IE such that no additional antibiotic therapy is required for the treatment of complicated bacteremia or IE.

   A patient will be defined as a clinical **Failure/Relapse** if any of the following criteria are met:

   - Ongoing signs and symptoms considered by the investigator to be related to complicated bacteremia or IE requiring additional antibacterial therapy
   - New onset of signs and symptoms of complicated bacteremia or IE after initial resolution at Day 42 (**Relapse**)
   - Recurrent bacteremia
   - Patient designated a clinical failure at Day 42
   - Death during the study period up to the visit
   - In the ITT population: If the patient had missing data at Day 42 such that a clinical outcome could not be determined and an imputation of outcome was not improved

4. Clinical outcome by pathogen at Day 42 and Day 84 in the ITT and CE populations (as described above in secondary efficacy assessments #1 and #3)

5. Microbiologic outcome by pathogen at Day 42 and Day 84 in the ITT and CE populations

   Microbiological outcome can be either **Microbiologic Success** or **Microbiologic Failure.**

   A patient will be defined as a **Microbiologic Success** if there is no further growth of baseline pathogen from blood cultures drawn at the Screening Visit up to the study visit.

   A patient will be considered as a **Microbiologic Failure** if any of the following criteria are met:

   - Persistent bacteremia defined as 2 consecutive positive blood cultures growing the baseline pathogen leading to the discontinuation of study drug
   - Subsequent isolation of the baseline pathogen from 2 consecutive blood cultures after initial clinical improvement (relapse)

9.5.2 Safety Assessments

Patients must be evaluated by a physician or an appropriately trained healthcare professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to 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 the purpose of the site's data collection responsibilities, any untoward event that was reported from the time the patient signed the ICF until the final protocol-defined study visit is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the investigator or other study center personnel

- All diseases that occur after signing the ICF, including any change in severity or frequency of pre-existing disease

- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note that hospital admissions and/or medical/surgical 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.

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 laboratory test finding should be noted in the eCRF.

The following events are captured as efficacy endpoints and are therefore excluded from AE reporting:

- 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. Events represented by the study endpoints include all of the following:

    - Worsening of signs and symptoms of complicated bacteremia or IE
    - Persistent bacteremia
    - Relapse of baseline bacteremia

9.5.2.2 Causality Assessment

For each AE, the investigator must provide an assessment of causal relationship to the investigational product. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the investigational product caused the event?

Yes: There is evidence to suggest a causal relationship between the investigational product and adverse event; ie:

- There is a reasonable temporal relationship between the investigational product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the investigational product and adverse event, ie:

- There is no reasonable temporal relationship between the investigational product and the event, or
- The patient did not take the investigational product, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or
- The event is commonly occurring in the (study) population independent of investigational product exposure

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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.5.2.4 Serious Adverse Events

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

- Results in death
- Is life threatening
- 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 1 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.

9.5.2.5 Medication Error

Medication error refers to any unintended error in the dosing and/or administration of the study drug as per instructions in the prescribing information. Medication errors generally fall into 4 categories as follows:

- wrong drug
- wrong dose (including dosing regimen, strength, form, concentration, amount);
- wrong route of administration;
- wrong patient (i.e. not administered to the intended patient)

Medication errors include occurrences of overdose and underdose of the investigational product.

9.5.2.6 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 center 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

For SAEs, the reporting period to the sponsor begins from the time that the patient signs the ICF 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.

9.5.2.7 Immediate Reporting of Serious Adverse Events

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.

All SAEs that occur in a patient from the time he or she signs the ICF until the last study visit must be reported to the sponsor within 24 hours of awareness of the event using the provided SAE Report Form. In addition to completing the SAE Report Form, each SAE must be entered on the appropriate page of the eCRF.

When death occurs with an SAE, the cause of death must be reported as an SAE. "Fatal" will be reported as the outcome for these events.

Within 24 hours of learning of any AE that meets 1 of the criteria for an SAE, the study site personnel must report the event to the sponsor 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 center to solicit additional information or follow up on the event.***

Fax the SAE Form for Clinical Trials to the following number:

[redacted]

9.5.2.8 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the patient signs the ICF until the final protocol-defined study visit. Within 24 hours of learning of the pregnancy, the study center personnel must report the event to the sponsor on the Clinical Trial Pregnancy Form and fax it to the SAE/Pregnancy fax number stated in Section 9.5.2.7, even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up 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 9.5.2.7 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Form.

9.5.2.9 Potential Hy's Law Cases

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

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limit of normal (ULN) AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study center 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 collected 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.

A laboratory alert for potential Hy's laws cases will be in place, and the laboratory must notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's law case must be faxed to the sponsor on an AE of Special Interest Form as soon as possible (within 24 hours of learning of the potential Hy's law case) to the SAE/Pregnancy fax number stated in Section 9.5.2.7, even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the medical monitor and in accordance with the FDA "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation" July 2009.

9.5.2.10 Clinical Laboratory Determinations

Blood samples for clinical laboratory tests will be collected at Screening (Visit 1), Baseline (Visit 2), Visit 4 (Day 22), Visit 5 (Day 42 s), and at the ET Visit. Urine samples will be collected at Baseline (Visit 2), Visit 3 (Day 8), Visit 4 (Day 22), Visit 5 (Day 42), Visit 6 (Day 84), and at the ET Visit for clinical laboratory tests. If not already collected per standard of care, at Screening (Visit 1) and Baseline (Visit 2), hematology and serum chemistry will also be done locally in order to qualify the patient for the study, in addition to being sent to the central lab. At Baseline (Visit 2), the investigator will assess the clinical significance of any values that are outside the reference ranges. Patients with abnormalities judged to be clinically significant will be excluded from the study.

Women of childbearing potential (including those who are fewer than 2 years postmenopausal) will be required to have urine/serum pregnancy tests at Screening (Visit 1) and Baseline (Visit 2) done locally to ensure the test is negative before randomization, and again at Visit 5 (Day 42) and at the ET Visit. If the serum test result cannot be obtained before randomization, a urine pregnancy test may be used for enrollment. Positive results on the pregnancy test will exclude patients from participating in the study.

The following clinical laboratory levels will be measured:

Hematology: Absolute and differential white blood cell (WBC) count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell (RBC) indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, lactate dehydrogenase, total and direct bilirubin, AST, ALT, and gamma-glutamyltransferase (GGT)

Urinalysis: Specific gravity, pH, protein, glucose, ketones, and blood nitrites, leukocyte esterase and microscopic exam (WBC, RBC, epithelial cells, bacteria or yeasts, casts, crystals)

Other: Pregnancy test, banked serum sample (3 mL serum sample for use in retrospective safety assessments or exploratory analyses, as needed), vancomycin levels in patients on vancomycin, to achieve serum trough concentrations of 10 to 15 µg/mL (for streptococci) or 10 to 20 µg/mL (for staphylococci), based on local standard of care.

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

9.5.2.10.1 Blood Samples for Culture

Peripheral blood cultures (aerobic and anaerobic) must be drawn at Screening, not through an existing intravascular line. When blood cultures are positive, they should be repeated once every 24 hours until negative. Blood cultures will be repeated at Day 1, 8, 22, 42, and 84 (and early termination). 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 daily upon knowledge of a positive result from any visit until clearance of bacteremia is confirmed.

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

Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility; microbiological specimens and isolates will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

9.5.2.10.2 Urine Samples for Culture

Urine cultures will be done at Day 1, 8, 22, 42, and 84 (and early termination). Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility; microbiological specimens and isolates will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

9.5.2.11 Vital Signs

Vital sign measurements will be documented at every visit. The parameters are blood pressure (BP), respiration rate, pulse rate, and temperature (oral, rectal, tympanic, or core). Pulse rate and BP readings will be taken after the patient has been sitting for 5 minutes.

9.5.2.12 Electro- and Echocardiograms

A 12-lead electrocardiogram (ECG) will be performed at Screening (Visit 1) and Day 8 (Visit 3) by a trained physician or health care professional. A transthoracic echocardiogram will be performed, or if clinically indicated, a transesophageal echocardiogram will be performed, unless one has been performed as standard of care for this episode of endocarditis. The overall interpretation and determination of the clinical significance of ECG findings will be the responsibility of the investigator, and the findings will be recorded in the patient's eCRF.

9.5.2.13 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 done at Screening (Visit 1) and at the ET Visit by a professionally trained physician or health professional licensed to perform physical examinations. A targeted physical examination will be done at Baseline (Visit 2), Visit 5 (Day 42), and Visit 6 (Day 84). Body weight and height will be measured at Screening (Visit 1). If height or weight is not obtainable (eg, patient is immobilized), the last known or stated height and weight may be used.

9.5.3 Dalbavancin Concentration Measurements

Blood samples for PK analyses will be collected at Visit 2 (Day 1) through Visit 5 (Day 42). 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.

Patients who receive dalbavancin who subsequently undergo valve surgery may have the option to have dalbavancin levels assessed in the resected valve tissue.

9.5.4 Health Economics and Outcomes Research Assessments

Details regarding healthcare resource utilization assessments can be found in Section 9.5.1.3.

9.5.5 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.0. The descriptions of the procedures to be performed at each visit are provided below.

9.5.5.1 Screening—Day -10 to Day 1 (Visit 1)

At Screening (Visit 1), the following procedures will be performed:

- Obtain informed consent
- Access IWRS and assign a unique PID number to the patient (Section 9.4.3)
- Confirm inclusion/exclusion criteria
- Obtain medical and surgical history
- Collect medication history (from 30 days prior to ICF signing)
- Collect blood samples for hematology and serum chemistry laboratory assessments
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse rate and BP readings will be taken after the patient has been sitting for 5 minutes.
- 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.

- Review and record AEs
- Perform ECG
- Perform pregnancy test for women of childbearing potential
- Collect results of echocardiography to confirm the diagnosis of endocarditis; perform an echocardiogram if it has not been done. Transthoracic echocardiogram or, if clinically indicated, transesophageal echocardiogram to be performed, unless one has been performed as standard of care for this episode of bacteremia/endocarditis.
- Collect blood cultures (aerobic and anaerobic), which should be drawn at Screening from 2 different anatomical sites and not through an existing intravascular line. When positive, blood cultures should be repeated once every 24 hours until negative. If clinically indicated, blood cultures should be collected at time of treatment discontinuation or for determination of treatment failure.
- Collect sample for banked serum (if feasible): 3 mL serum sample for use in retrospective safety assessments or exploratory analyses, as needed

9.5.5.2 Baseline—Day 1 (Visit 2)

The Baseline Visit (Visit 2) will be conducted within 10 days of Screening (Visit 1) after having confirmed defervescence for at least 24 hours and clearance of bacteremia from the qualifying pathogen (at Screening), with negative blood culture incubated for at least 72 hours (5 days for slow-growing fastidious gram-positive organisms). Study procedures will then be reviewed with the patient and the caregiver, if applicable.

At Baseline (Visit 2), the following procedures will be performed:

- Review inclusion/exclusion criteria
- Review medical and surgical history
- Review medication history (between Visit 1 and Visit 2) and concomitant medications (medications post first dose of investigational product)
- Access IWRS
- Randomization
- Review and record AEs

- Measure and evaluate vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse rate and BP readings will be taken after the patient has been sitting for 5 minutes.
- Perform targeted physical examination
- Collect blood samples for hematology and serum chemistry laboratory assessments
- Collect blood cultures, urinalysis, and urine cultures
- Collect sample for banked serum (if feasible): 3 mL serum sample for use in retrospective safety assessments or exploratory analyses, as needed
- Perform pregnancy test for women of childbearing potential
- For patients on dalbavancin: collect blood samples for PK analyses, 2-4 hours after start of infusion
- Administer IV investigational product therapy according to randomization. For patients randomized to standard of care antibiotic therapy, IWRS should be accessed to obtain investigational product assignments per dosing frequency and duration in Section 9.4.1.2. Access to IWRS is required to dispense Dalbavancin. Additional IWRS access for standard of care antibiotic therapy is required based on site requirement.
- Document investigational product compliance
- Collect healthcare resource utilization data
- Assess HRQoL by administering Form SF-12

9.5.5.3 Visit 3 (Day 8)

At Visit 3 the following procedures will be performed:

- Access IWRS
- Review and record AEs
- Measure and evaluate vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse and BP readings will be taken after the patient has been sitting for 5 minutes.
- Perform ECG

- Collect blood cultures, urinalysis, and urine cultures
- For patients on dalbavancin: collect blood samples for PK analyses at predose and 2-4 hours after start of infusion
- Review concomitant medications
- Review concomitant nondrug interventions
- Administer IV investigational product therapy according to randomization and document compliance.
- Collect healthcare resource utilization data
- Collect patient satisfaction question (1-item survey); Question 2b in Appendix 4

9.5.5.4 Visit 4 (Day 22 ± 1 day)

At Visit 4 the following procedures will be performed:

- Review and record AEs
- Measure and evaluate vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse rate and BP readings will be taken after the patient has been sitting for 5 minutes.
- Collect blood samples for hematology and serum chemistry laboratory assessments
- Collect blood cultures, urinalysis, and urine cultures
- For patients on dalbavancin: collect blood samples for PK analyses when subject is at clinic (record PK collection date and time)
- Review concomitant medications
- Review concomitant nondrug interventions
- Administer IV investigational product therapy according to randomization and document compliance.
- Collect healthcare resource utilization data
- Collect patient satisfaction question (1-item survey); Question 2b in Appendix 4

9.5.5.5 Visit 5 (Day 42 ± 3 days)

At Visit 5, the following procedures will be performed:

- Review and record AEs
- Measure and evaluate vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse and BP readings will be taken after the patient has been sitting for 5 minutes.
- Collect blood samples for hematology and serum chemistry laboratory assessments
- Collect blood cultures, urinalysis, and urine cultures
- For patients on dalbavancin: collect blood samples for PK analyses when subject is at clinic (record PK collection date and time)
- Collect sample for banked serum (if feasible): 3 mL serum sample for use in retrospective safety assessments or exploratory analyses, as needed
- Perform targeted physical examination
- Perform pregnancy test for women of childbearing potential
- Review concomitant medications and concomitant nondrug interventions
- Administer IV investigational product therapy according to randomization and document compliance
- Complete investigator assessment of efficacy
- Collect healthcare resource utilization data
- Collect full patient satisfaction questionnaire in Appendix 4; if not collected at Visit 5 collect at ET
- Collect provider satisfaction question (1-item survey); Appendix 5
- Assess HRQoL by administering Form SF-12

9.5.5.6 Visit 6 (Day 84 ± 7 days)

At Visit 6 (Day 84), the following procedures will be performed:

- Review and record AEs

- Measure and evaluate vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse rate and BP readings will be taken after the patient has been sitting for 5 minutes.
- Perform targeted physical examination
- Collect blood cultures, urinalysis, and urine cultures
- Review concomitant medications and concomitant nondrug interventions
- Complete investigator assessment of efficacy
- Collect healthcare resource utilization information

9.5.5.7 Early Termination Visit

At the Early Termination Visit, the following procedures will be performed:

- Review and record AEs
- Collect blood samples hematology and serum chemistry laboratory assessments
- Collect blood cultures, urinalysis, and urine cultures
- Measure and evaluate vital signs (blood pressure, respiration rate, pulse rate, and temperature [oral, rectal, tympanic, or core]). Pulse and BP readings will be taken after the patient has been sitting for 5 minutes.
- Perform complete physical examination
- Perform pregnancy test for women of childbearing potential
- Review concomitant medications and concomitant nondrug interventions
- Document investigational product compliance
- Collect healthcare resource utilization information
- Assess HRQoL by administering Form SF-12
- Collect patient satisfaction question (1-item survey), Question 2b in Appendix 4; or collect full patient satisfaction questionnaire if not collected at Visit 5 (Day 42 ± 3 days)

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 Monitoring

Before any patient enters the study, a representative of the sponsor will meet with the investigator and the study center staff to review the procedures to be followed during the study. Electronic data capture (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 center 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 center 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.

9.6.2 Data Recording and Documentation

Data collection will involve the use of the sponsor's 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 edits checks, data monitoring, reviews, and queries may be electronically issued to the site and should be answered electronically via the EDC system.

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

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

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

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Patient Populations

Five populations will be considered in the statistical analysis of the study.

9.7.1.1 Screened Population

The screened population will consist of all patients who undergo the Screening Visit (Visit 1) and receive a PID number.

9.7.1.2 Intent-to-Treat/Randomized Population

The intent-to-treat (ITT) population will consist of all randomized patients regardless whether or not they received study treatment.

9.7.1.3 Safety Population

The safety population will consist of all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed based on the treatment received.

9.7.1.4 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will consist of all patients in the ITT population who received at least one dose of study drug.

9.7.1.5 Clinically Evaluable Population

The clinically evaluable (CE) population will consist of all patients in the mITT population who met criteria for clinical evaluability.

9.7.2 Patient Disposition

The number of patients in 4 of the study populations (ITT, Safety, mITT, and CE) will be summarized by treatment group and study center; the screened population will only be summarized by study center.

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 (up to Day 42) 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 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

Demographic parameters (ie, age, race, ethnicity, sex, weight, height, body mass index) and other baseline characteristics will be summarized by treatment group for the Safety and ITT populations. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients. The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the ITT population.

Prior medication is defined as any medication taken before the date of the first dose of investigational product. Concomitant medication is defined as any medication started on or after the date of the first dose of investigational product.

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. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to investigational product for the safety population will be summarized for treatment duration, calculated as the number of days from the date of the first dose of investigational product administered to the date of the last dose administered, inclusive. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

The following parameters for the daily dose of investigational product will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum).

9.7.4.2 Measurement of Treatment Compliance

Treatment compliance for a specified period is defined as the total number of doses of IV therapy actually administered to a patient during that period divided by the number of doses of IV therapy that were expected to be administered during the same period multiplied by 100. Descriptive statistics for investigational product compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the whole treatment period of the study for the safety population.

9.7.5 Efficacy Analyses

Efficacy analyses will be based on the ITT analysis set. For all efficacy analyses, the baseline is defined as Day 1 before dosing. Missing data will be imputed as failure for the primary efficacy analysis. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

9.7.5.1 Primary Efficacy Parameters

The primary efficacy endpoint is the number and percentage of patients with outcomes of success and failure at Day 84 poststudy entry (test of cure), consisting of a maximum of 6 weeks of therapy postrandomization, plus a 6 week follow-up period to detect relapse until test of cure in the ITT population.

For the primary endpoint, the number and percentage of patients with outcomes of success and failure in the ITT population will be determined in each treatment group. The noninferiority hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance with a noninferiority margin of 10%. The observed difference in percentage of success at Day 84 (dalbavancin group minus the standard of care antibiotic therapy group) will be determined and a 95% CI for the observed difference will be computed using the method proposed by Miettinen and Nurminen (Miettinen 1985), which corresponds to the p-value approach of the Farrington-Manning test (Farrington 1990). If the lower limit of the 95% CI for the difference in improvement rates in the ITT population is greater than -10%, the noninferiority of dalbavancin to standard of care antibiotic therapy will be concluded.

9.7.5.2 Secondary Efficacy Parameters

The following are secondary efficacy endpoints:

- Percentage of patients with clinical outcome of success at Day 42 in the ITT and CE populations
- Mortality at Day 84 after the initiation of study drug therapy in the safety population
- Percentage of patients with clinical outcome of success at Day 84 in the CE population
- Percentage of patients with clinical outcome of success by pathogen at Day 42 and Day 84 in the ITT and CE populations
- Percentage of patients with microbiologic success by pathogen at Day 42 and Day 84 in the ITT and CE populations.

For secondary efficacy endpoints, 2-sided 95% CIs for the treatment difference between 2 groups will be provided using the method proposed by Miettinen and Nurminen (Miettinen 1985). Descriptive statistics, including number and percentage for the categorical variables, will be provided by treatment group.

[redacted]

9.7.6.1 Adverse Events

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

The number and percentage of patients reporting treatment-emergent AEs 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 treatment-emergent AEs by severity and causal relationship to the investigational product will be summarized by treatment group. For health economics and outcomes research (HEOR) data, the number of AEs associated with the PICC line will be determined.

The incidence of common (≥ 2% of patients in any treatment group) treatment-emergent AEs, 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 investigational product. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred during or after the first infusion of investigational product.

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

9.7.6.2 Clinical Laboratory Parameters

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

The number and percentage of patients with potentially clinically significant (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 potential Hy's law criteria will be summarized for the safety analysis set. Supportive tabular displays will also be provided. See Section 9.5.2.9.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic BP) 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, study center 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.

9.7.6.4 Electrocardiogram

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and changes from baseline values at each assessment time point will be presented by treatment group. The QTc interval is calculated using both the Bazett ($QTcB = QT/[RR]^{1/2}$) and Fridericia ($QTcF = QT/[RR]^{1/3}$) corrections.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated by treatment group. The criteria for PCS ECG 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 ECG values will also be provided.

9.7.6.5 Dalbavancin Plasma PK Parameters

Descriptive summary statistics will be provided for dalbavancin plasma PK parameters.

9.7.7 Health Economics and Outcomes Research Analyses

Healthcare resource utilization assessments are described in detail in Sections 9.5.1.3 and 9.7.5.3.

[redacted]

9.7.9 Determination of Sample Size

Assuming a point estimate for the primary outcome measure of clinical success rate of 90% in the dalbavancin treatment group and 83% in the standard of care treatment group, a noninferiority margin of 10%, a 1-sided Type I error of 0.025, and power of approximately 85%, a total sample size of 150 patients is required with 2:1 randomization ratio (100 patients in dalbavancin treatment group and 50 patients in standard of care treatment group). The randomization will be stratified based on screening pathogen: MSSA, MRSA, or streptococci.

9.7.10 Computer Methods

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

9.7.11 Adjudication Committee

An independent, blinded adjudication committee will be used to review the data from each patient to establish the baseline diagnosis, final diagnosis, and final outcome, including reasons for treatment failure.

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/IEC and the signature page, signed by the investigator, has been received by the sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS AND VIOLATIONS

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/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing, or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, 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 should 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/IEC must be notified according to the criteria and time period dictated by the IRB/IEC associated with this study.

10.0 STUDY SPONSORSHIP

This study is sponsored by Allergan Pharmaceuticals International Ltd.

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 SOP on publications.

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The investigator must provide the following to the sponsor before the start of the study:

- A completed and signed Form FDA 1572 for sites in the United States only. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae for the investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 5.1
- A copy of the IRB/IEC-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/IEC members or the DHHS general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the investigator
- Financial disclosure agreement completed and signed by the investigator and all sub-investigators listed on Form FDA 1572. The investigator and all sub-investigators will provide an updated financial disclosure agreement to the sponsor 1 year after the completion of the study

11.2 PERFORMANCE

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

11.3 USE OF INVESTIGATIONAL MATERIALS

The investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the investigator or sub-investigators listed on Form FDA 1572. 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.

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 case report forms, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and ECGs) 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.

For Canadian study centers only: All records and documents pertaining to the conduct of the study must be retained for a 25-year period in accordance with the Canadian Food and Drugs Act and Regulations.

11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by 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 (DAL-MD-09, dated 19 October 2016) and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____
Investigator's Signature Date

_____
Investigator's Name

13.0 APPENDICES

APPENDIX 1. 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, 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. (In some cases, it may be necessary to identify a person other than the investigator as the contact. The guidance of the IRB/IEC may be required)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation

- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient

- The approximate number of patients involved in the study

- A statement of consent (eg, "I agree to participate . . .")

- A place for the patient's signature and date of signing

- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

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

APPENDIX 2. CONTACT INFORMATION

Contact information for sponsor personnel is as follows:

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

APPENDIX 3. METHOD FOR DETERMINATION OF CREATININE CLEARANCE

Creatinine clearance should be determined by the method of Cockcroft-Gault based on serum creatinine concentrations obtained at Baseline, using ideal body weight instead of actual weight.

For males:

Glomerular filtration rate (GFR) = [(140 – age) × (Ideal body weight in kg)] / (72 × Cr)

For females:

GFR = [(140 – age) × (Ideal body weight in kg) × 0.85] / (72 × Cr)

Ideal body weight is calculated as:

For males:

If height (H) > 152.5 cm

Ideal body weight = 50 + [(H – 152.4) × 0.89]

If H < 152.5 cm

Ideal body weight = 50 – [(152.4 – H) × 0.89]

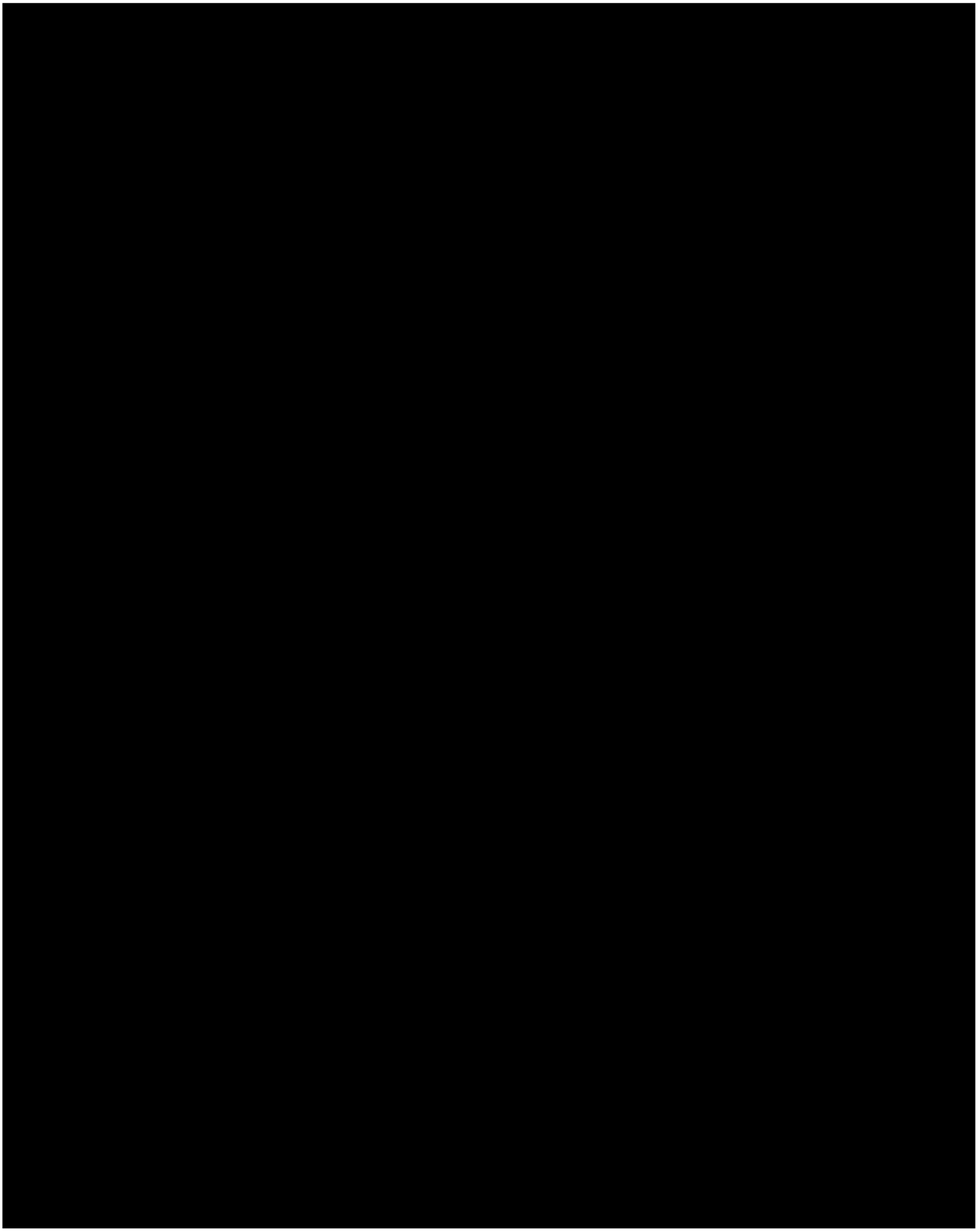
For females:

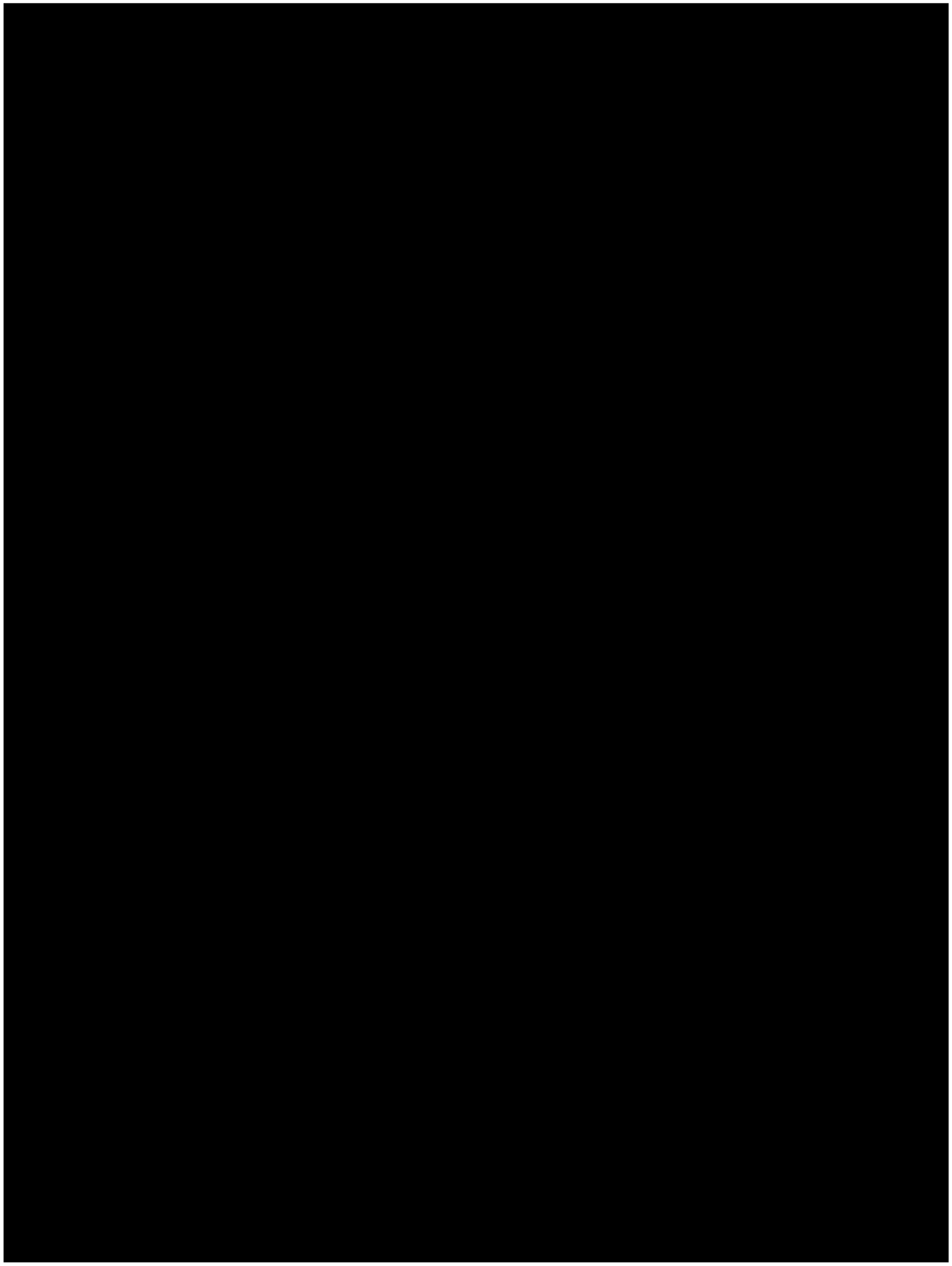
If H > 152.5 cm

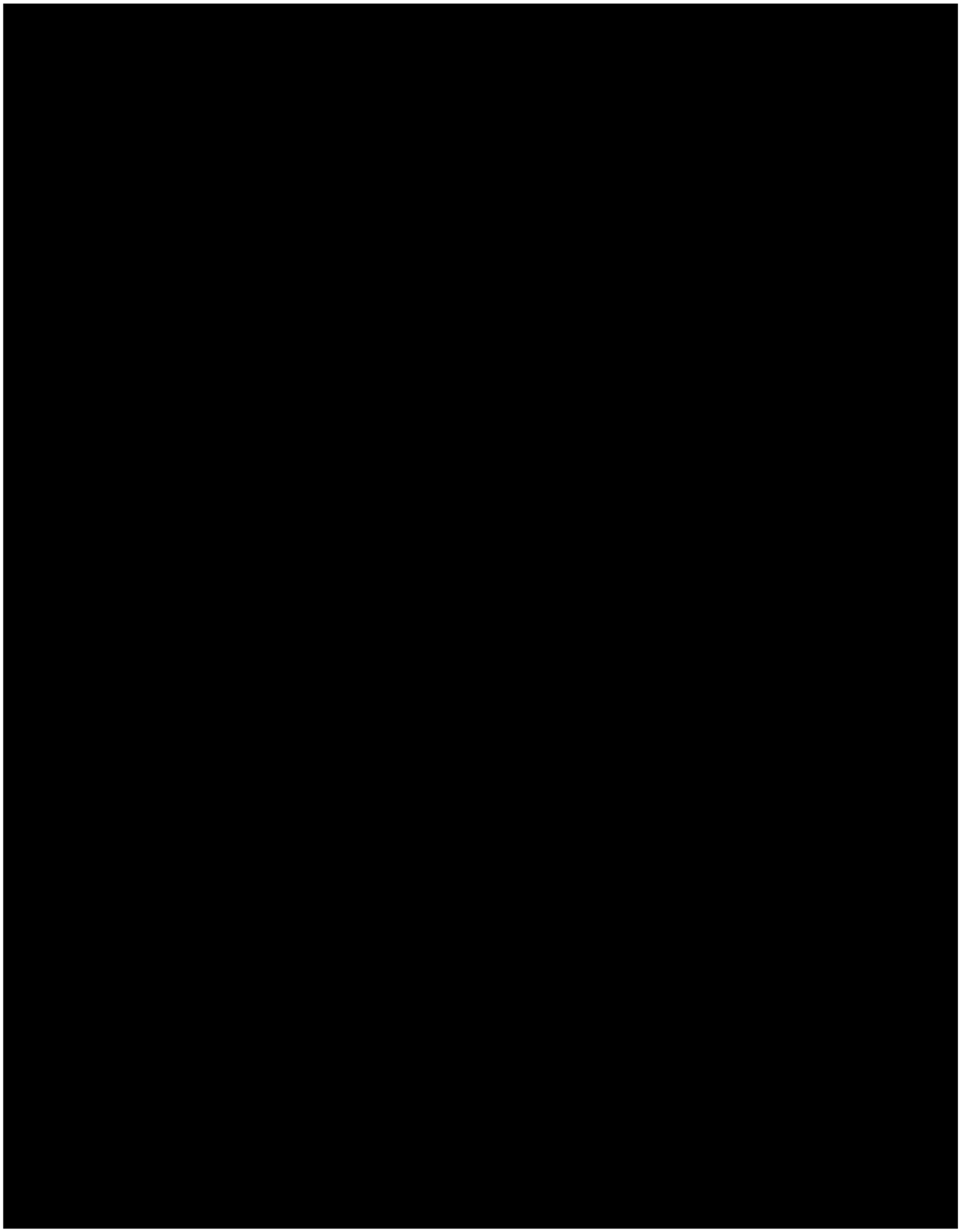
Ideal body weight = 45.4 + [(H – 152.4) × 0.89]

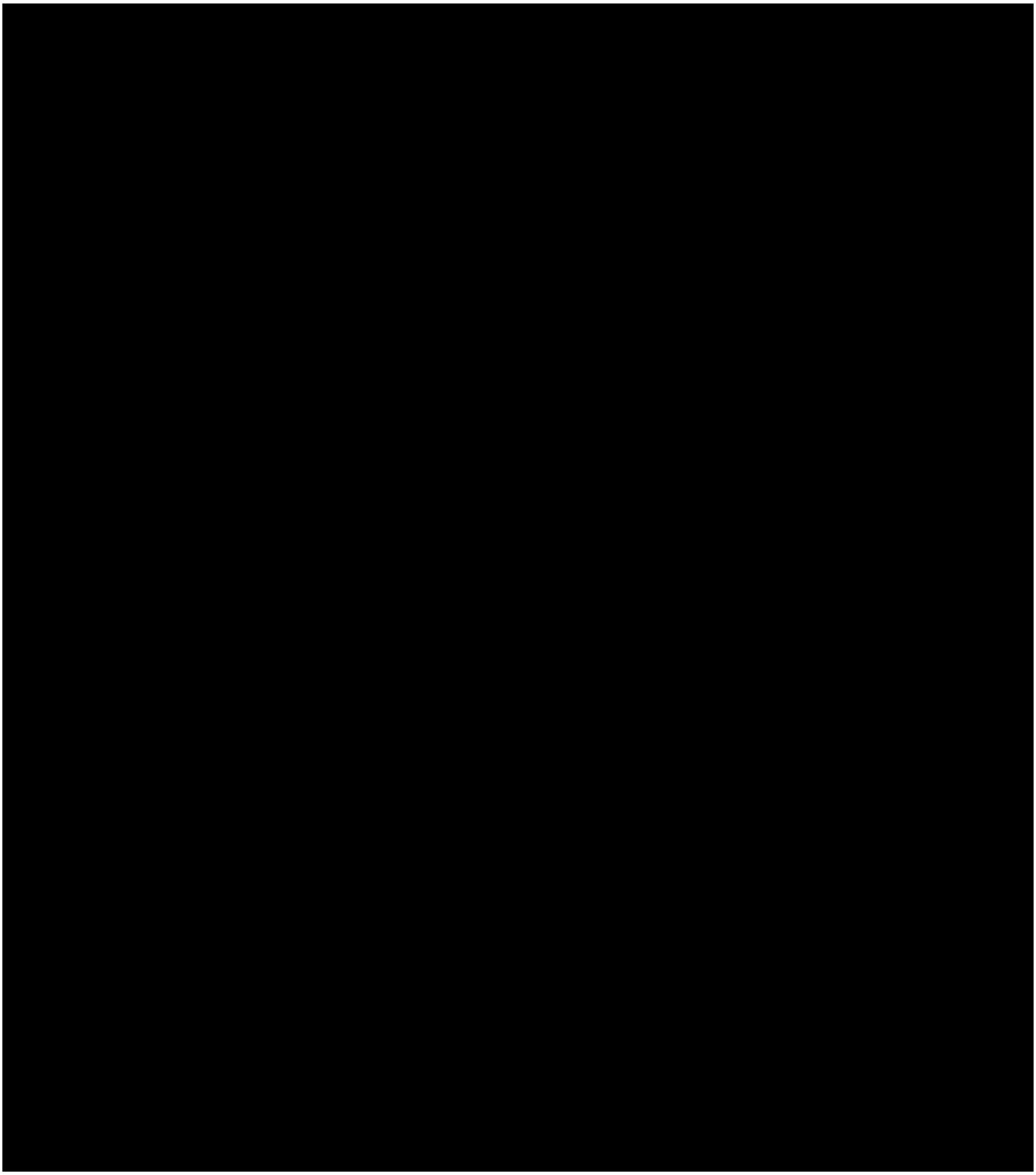
If H < 152.5 cm

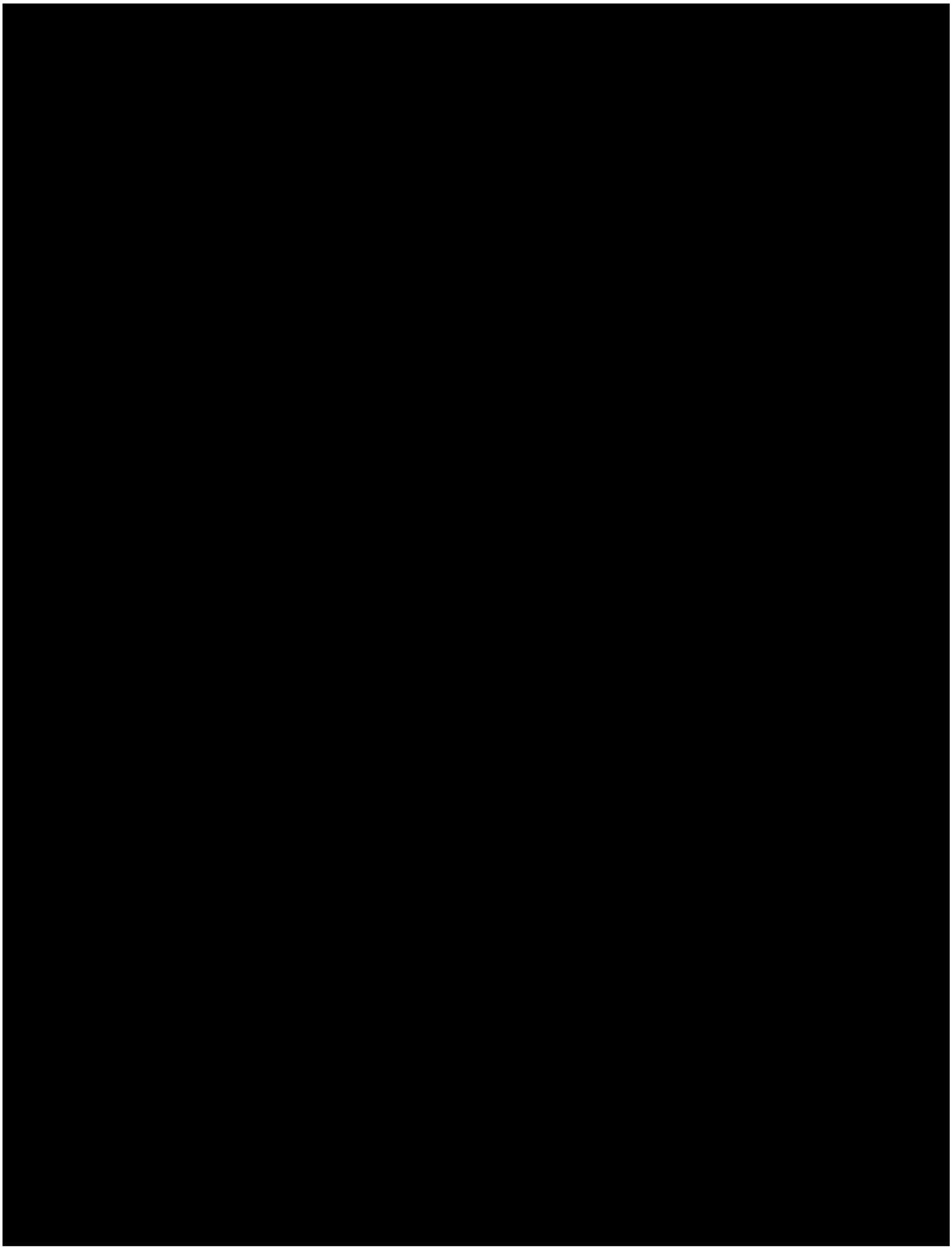
Ideal body weight = 45.4 – [(152.4 – H) × 0.89]

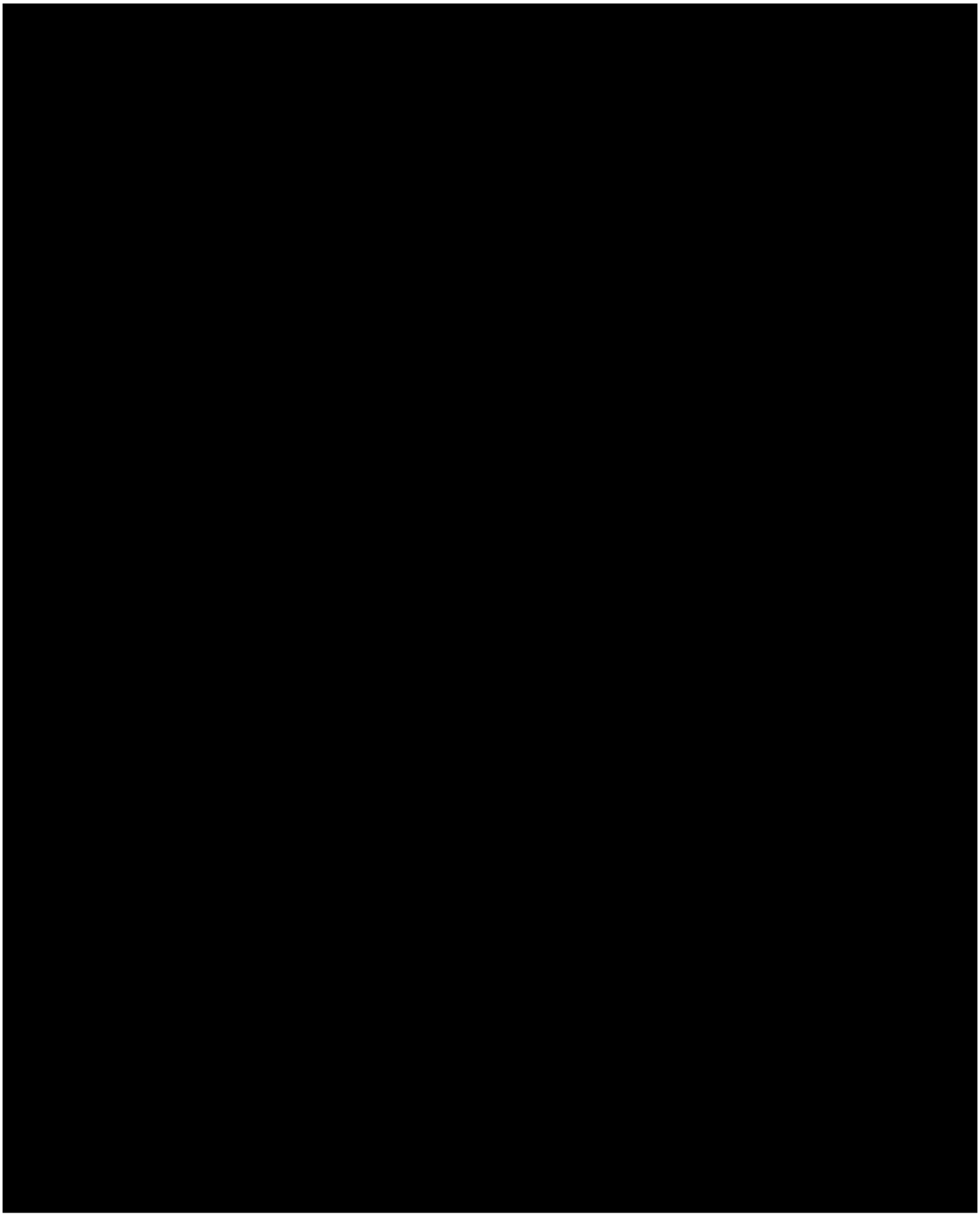


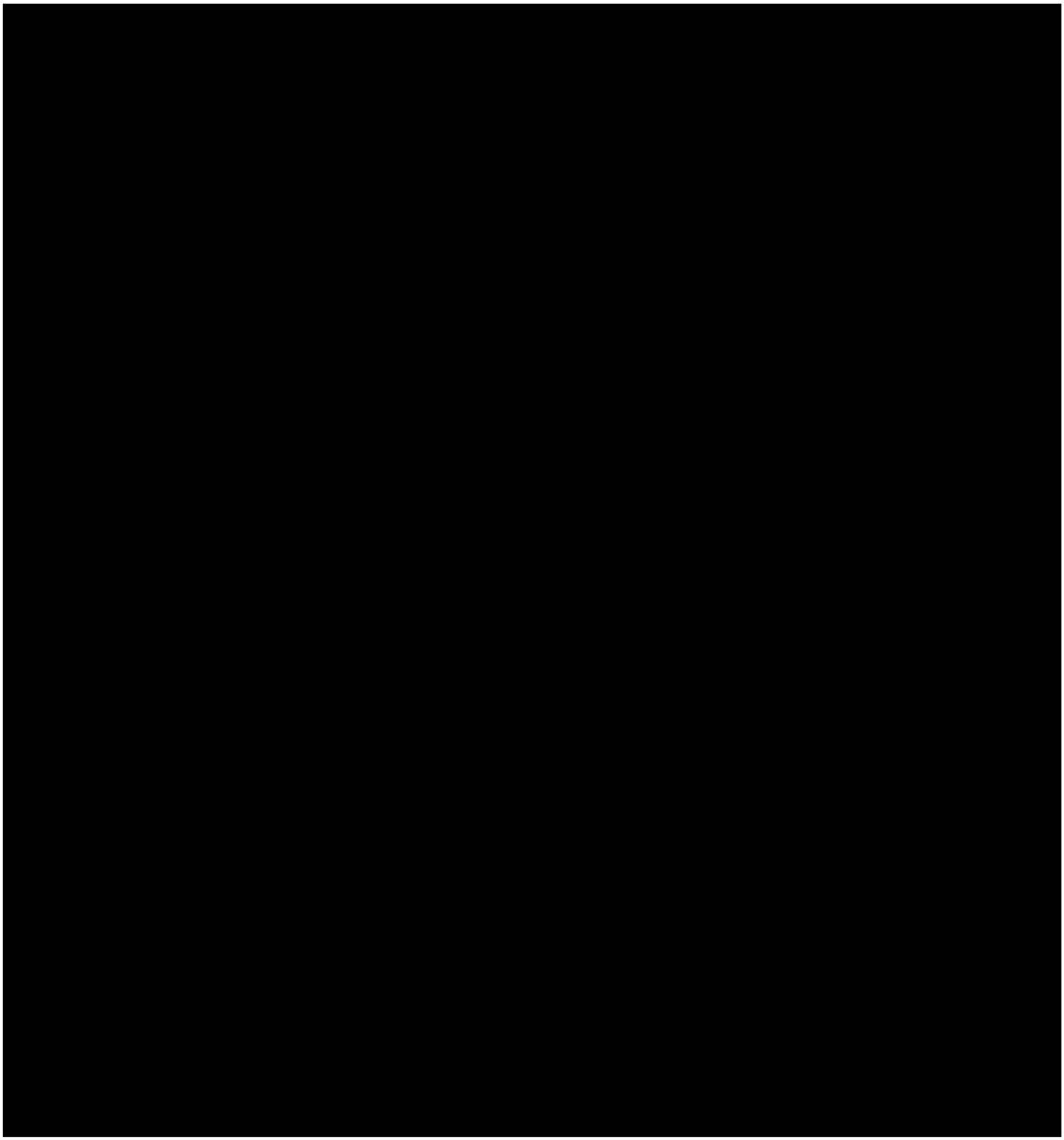


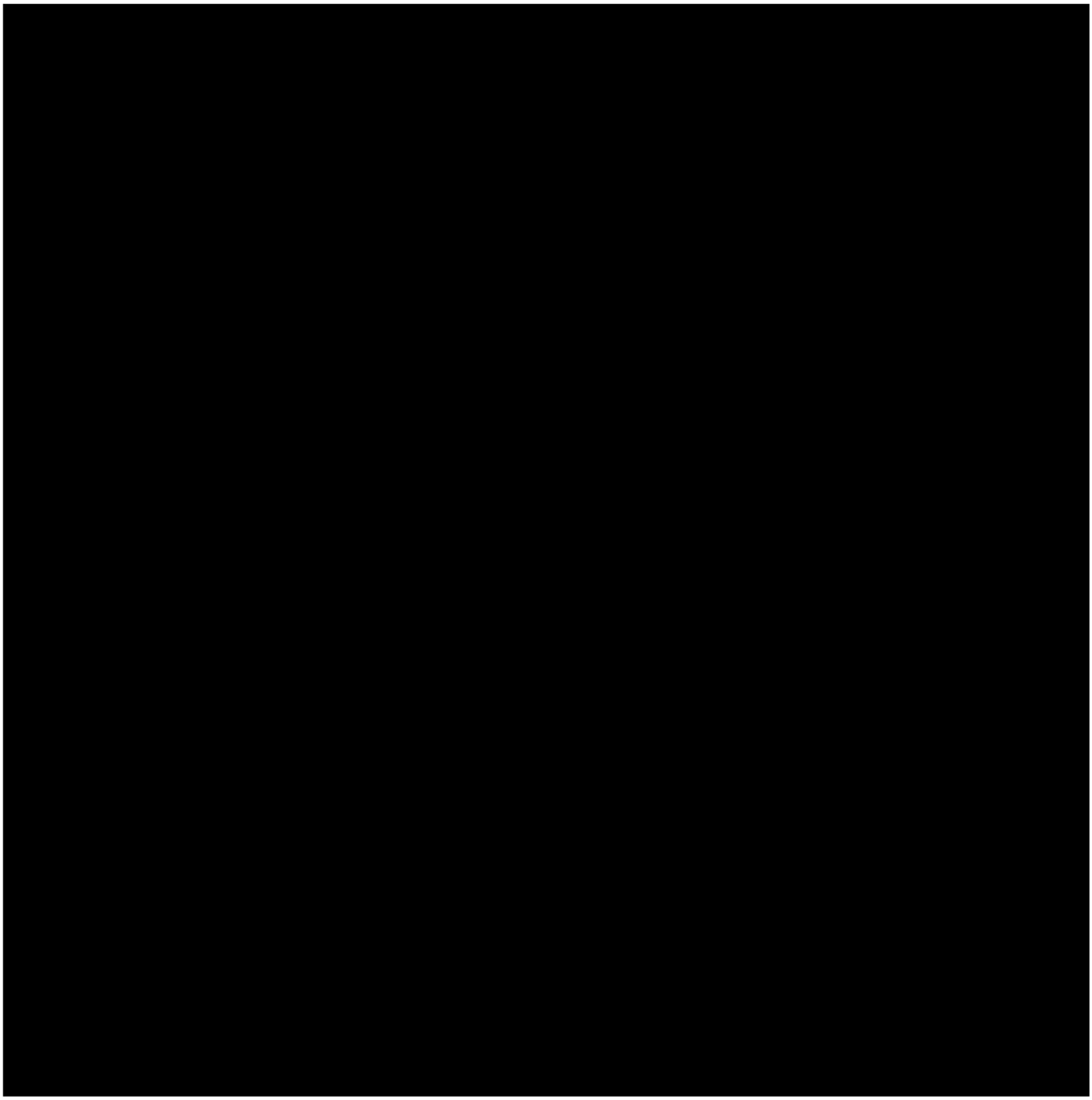


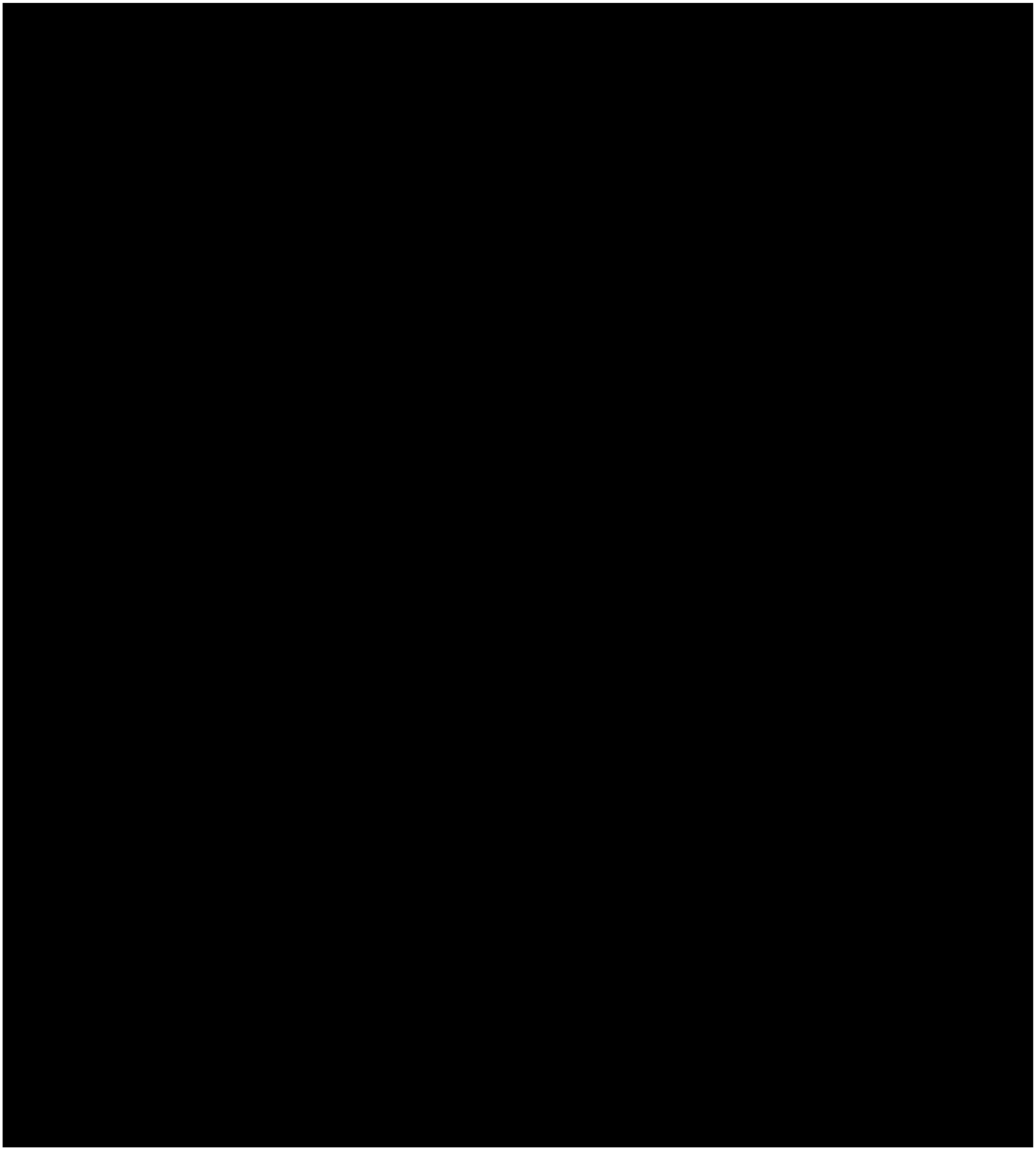


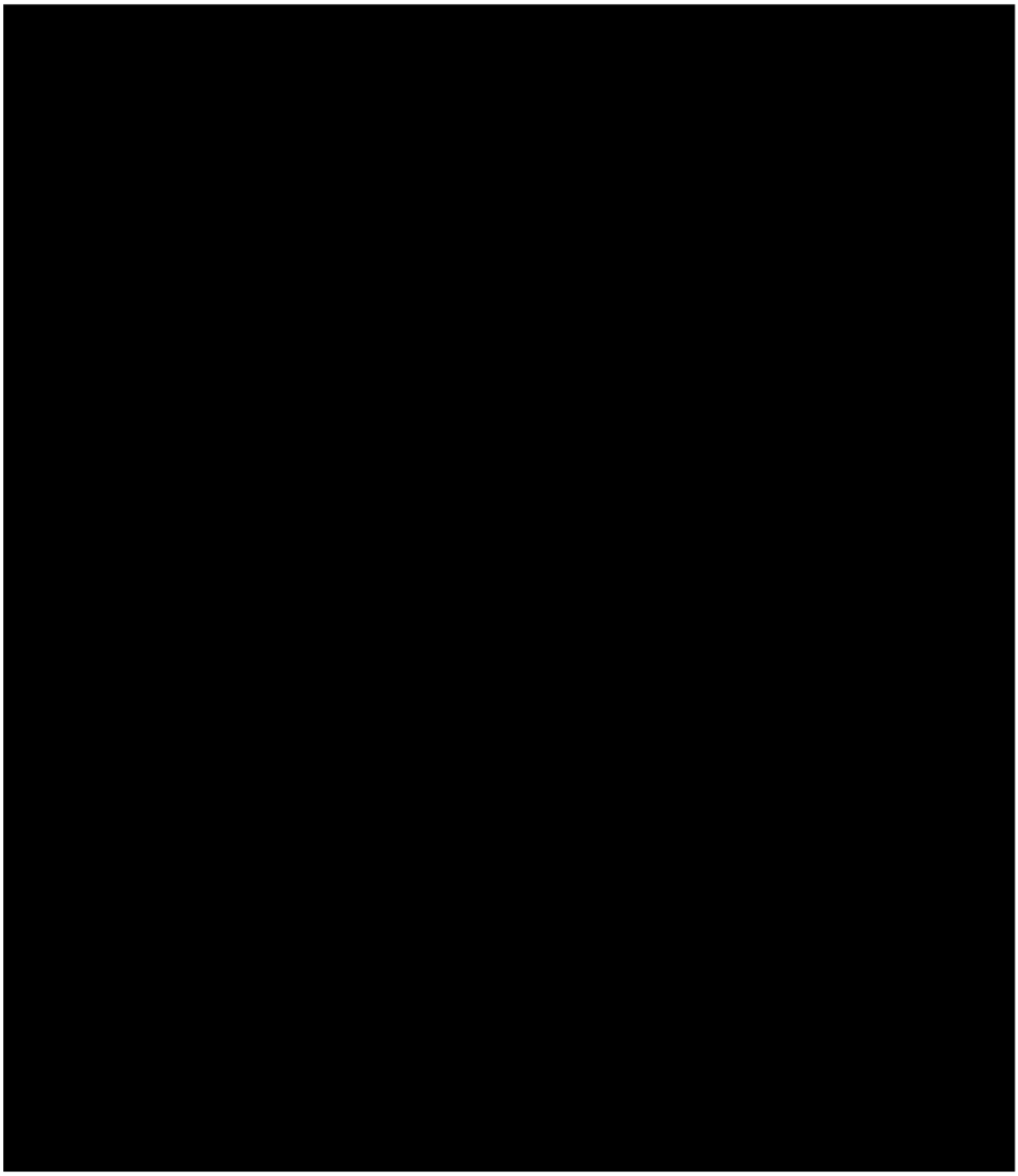


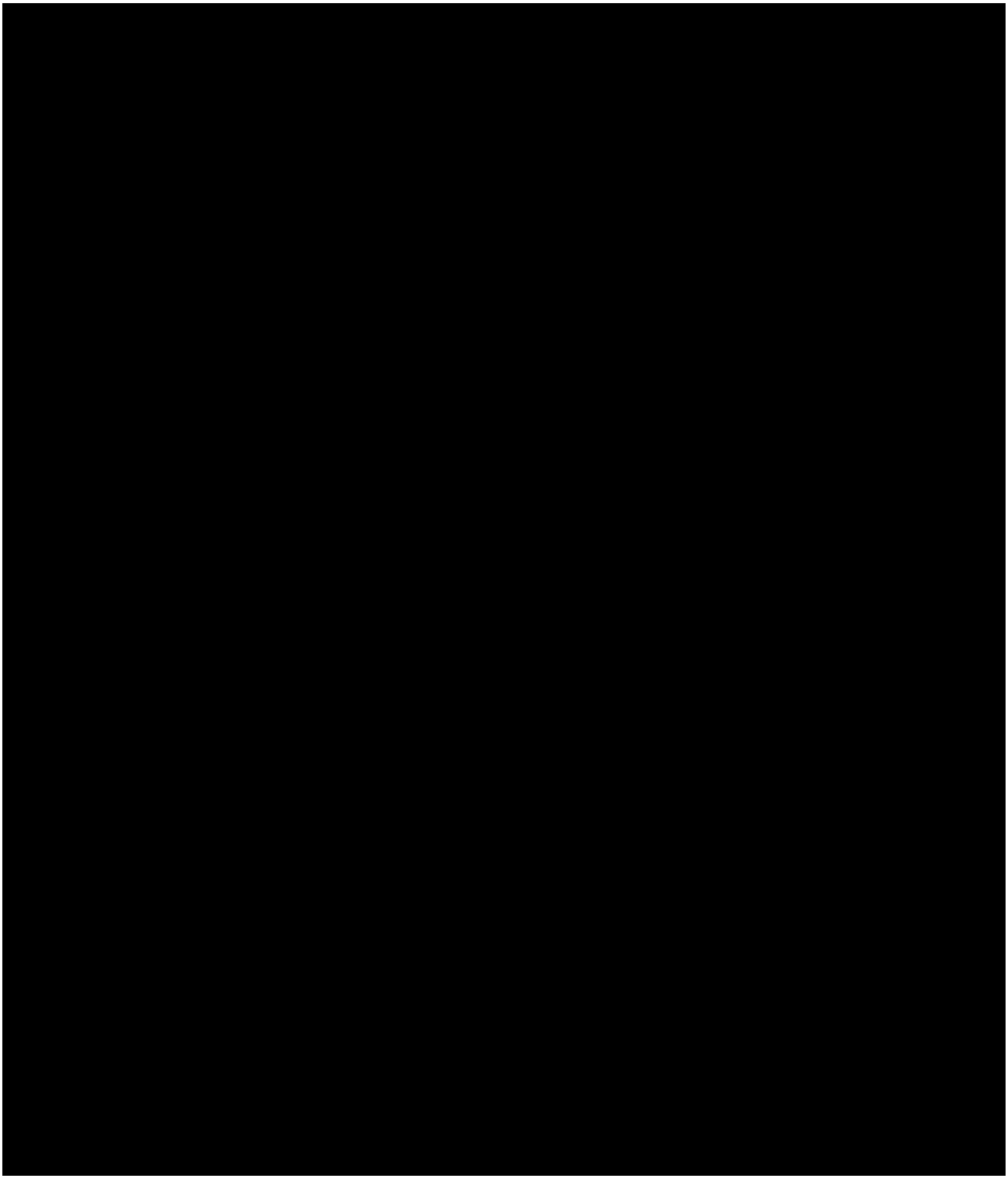












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