STATISTICAL ANALYSIS PLAN

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telavancin, Study 0112

A Phase 3 Multicenter, Randomized, Open-label, Clinical Trial of Telavancin Versus Standard Intravenous Therapy in the Treatment of Subjects with Staphylococcus aureus Bacteremia Including Infective Endocarditis

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ADAM	Analysis data model
AE	adverse event
AT	All-treated (analysis population)
BLQ	Below level of quantification
BMI	body mass index
BP	blood pressure
CB	complicated bacteremia
CI	confidence interval
CFB	change from baseline
CP	conditional power
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end-of-treatment
HR	heart rate
IDMC	Independent Data Monitoring Committee
IEAC	Independent Efficacy Adjudication Committee
IV	intravenous
LIE	left-sided infective endocarditis
LOD	limit of detection
mAT (CB, RIE)	mAT subjects with a diagnosis of CB, or RIE
mAT (UCB, CB, RIE)	mAT subjects with a diagnosis of UCB, CB, or RIE (the primary analysis population)
MedDRA	Medical Dictionary for Regulatory Activities
NC	non-calculable
NQ	non-quantifiable
PENSAB	Potentially effective non-study antibiotic
PK	pharmacokinetic
PP	Per-protocol
PT	preferred term
QBC	qualifying blood culture
RIE	right-sided infective endocarditis
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TEE	transesophageal echocardiogram

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
TOC	test-of-cure
TTE	transthoracic echocardiogram
UCB	Uncomplicated bacteremia
WHODD	World Health Organization Drug dictionary

1 INTRODUCTION

This document outlines the initial plan for the summarization and analysis of clinical data collected in Study 0112 for telavancin.

The analysis of pharmacokinetics (data derivation and summary of individual PK parameters) is outside the scope of this document and is not addressed here.

This document describes the a priori plan for analysis. Once the analysis is in progress, it may become apparent from the data that the planned analysis should be modified. Any substantive modification to the original analysis plan will be identified in the clinical study report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is:

- To compare telavancin to standard IV therapy (ie, vancomycin, daptomycin, anti-staphylococcal penicillin, or cefazolin) in clinical outcomes in the treatment of S. aureus bacteremia including S. aureus right-sided infective endocarditis (RIE).

2.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of telavancin compared with standard intravenous therapy in the treatment of S. aureus bacteremia, including SA-RIE,
- To evaluate the PK profiles of telavancin and vancomycin in subjects with S. aureus bacteremia, including SA-RIE.

3 OVERVIEW OF STUDY DESIGN

3.1 Study Design

This is a multicenter, randomized, open-label, noninferiority trial of telavancin versus standard intravenous (IV) therapy control (ie, vancomycin, daptomycin, or a β-lactam antibiotic with anti-staphylococcal activity [eg, nafcillin, oxacillin, and cefazolin]) in the treatment of subjects with *S. aureus* bacteremia and *S. aureus* RIE.

The primary efficacy endpoint is clinical outcome at the test-of-cure (TOC) visit analyzed in subjects with a baseline diagnosis of complicated bacteremia (CB), uncomplicated bacteremia (UCB), or RIE in the microbiological all-treated (mAT) population.

The baseline diagnosis and the clinical outcome will be adjudicated by a blinded Independent Efficacy Adjudication Committee (IEAC). Safety will be monitored by an Independent Data Monitoring Committee (IDMC).

3.2 Study Procedures

Eligible subjects with confirmed *S. aureus* bacteremia will be randomized in a ratio of 1:1 to receive open-label telavancin or open-label standard IV therapy. Randomization will be stratified by geographic region. Standard IV therapy, depending on the antibacterial susceptibility of the causative pathogen, will include vancomycin or daptomycin for subjects with known or suspected MRSA (daptomycin should be used for subjects with *S. aureus* with vancomycin MIC values >1 µg/mL); or a protocol-specified β-lactam antibiotic with anti-staphylococcal activity (ie, nafcillin, oxacillin, cloxacillin, or cefazolin) for subjects with known MSSA.

Each subject must have at least one blood culture positive for S. aureus within 48 hours before randomization, referred to as the qualifying blood culture (QBC).

Procedures to control or eliminate the infection source will be completed within the first 3 days of study drug treatment. Follow-up blood cultures will be performed daily until two successive post-randomization blood cultures are negative for S. aureus.

On or before Day 8, each subject will be evaluated by a physician investigator to determine the origin and extent of the *S. aureus* infection to establish the classification of infection type as:

- Uncomplicated bacteremia (UCB),
- Complicated bacteremia (CB),
- Right-sided infective endocarditis (RIE), or,
- Left-sided infective endocarditis (LIE).

Subjects will be assigned to receive therapy based on the classification of infection type (see Table 1).

Subjects who are discharged from the hospital during the treatment or follow-up period, will return to the hospital once per week for a study visit.

After all the weekly visits are complete, the subject will also return to the hospital for the End of Therapy Visit, the Post-End of Treatment Visit, and the TOC visit. The TOC visit is also the end of study (EOS).

Development of new signs or symptoms consistent with *S. aureus* infection will be assessed daily, during the hospital stay, or during the study drug treatment period as clinically indicated. After Day 8, if signs and symptoms lead to a subsequent confirmed diagnosis of new metastatic foci, it will be criteria for clinical failure.

Study visits for endpoint assessment will be conducted as follows:

- End of therapy (EOT) visit: within 3 days after the last dose of study drug
- A post-EOT blood culture will be obtained at least 4 days after the EOT visit, and results must be available prior to the TOC visit. The results of this blood culture will be part of the assessment of clinical outcome at TOC.
- Test of cure (TOC) visit timing was defined by the classification of infection type, assigned treatment duration, and Study Protocol version (see Table 1).

3.3 Protocol Amendments

Study Protocol was originally finalized on 12 September 2014. The protocol underwent four major amendments finalized on 17 February 2015, 14 September 2015, 21 September 2016, and 16 January 2018.

Subjects could have consented to a more recent version of the Study Protocol during the study participation. The most recent version of the protocol consented to by Study Day 8 was used to determine the applicable protocol version for any assessments after the first dose of study drug. The original version was applicable for screening assessments (eg, eligibility criteria).

Requirements for study treatment duration and the timing of follow up assessments changed with Study protocol Amendment 2, and again with Amendment 3.

Table 1: Overview of Protocol Requirements for Treatment Duration and TOC Visit Windows

Protocol Version	Subject Classification	Treatment Duration		TOC Visit Window[a]
		Minimum	Maximum	
Original/ Amendment 1	Assigned 4 weeks of treatment	Not specified	Not specified	56±2 days
	Assigned 6 weeks of treatment	Not specified	Not specified	70±2 days
Amendment 2	UCB	2 weeks	4 weeks[b]	42±2 days
	CB	4 weeks	6 weeks[b]	56±2 days
	LIE/RIE	6 weeks	6 weeks[b]	70±2 days
Amendment 3	UCB	2 weeks	4 weeks[b]	38±2 days
	CB	4 weeks	6 weeks[b]	52±2 days
	LIE/RIE	6 weeks	6 weeks[b]	

a TOC visit windows were specified in the protocol as days from or after randomization

b treatment durations longer than 28 days for UCB, 42 days for CB, or 45 days for LIE or RIE would render subject's outcome failure (at TOC)

The EOT visit was to occur within 3 days after study drug discontinuation in all versions of the protocol.

An interim analysis allowing stopping for futility was introduced in Study Protocol Amendment 4.

3.4 Blinding of the Sponsor Clinical Team

While the study is open label, the following steps have been taken to establish blinding of the clinical team at Theravance, as of June of 2017.

- Notifications of randomization sent to Theravance by an Independent Randomization Technology system were stopped.
- Pharmacokinetic sample collection, treatment assignment, and treatment administration information has been excluded from the clinical data base extracts sent to Theravance.
- Tables and listings produced for internal safety and data monitoring exclude treatment assignments.
- Only open session IDMC reports, meeting minutes, and recommendations were routinely shared with Theravance; open reports present data in a blinded fashion, with data pooled.

3.5 Interim Analysis

A single interim assessment allowing early stopping for futility will be performed based on the subjects who discontinued from the study on or before October 31, 2017. Conditional power to show non-inferiority under the current trend will be computed using the normal approximation to the non-inferiority test statistic. The IDMC may recommend stopping for futility, if the conditional power is 50% or less.

At the interim analysis, a decision was made by the company to discontinue further enrollment in the study when viewing the overall study costs within the overall portfolio of the company.

4 SAMPLE SIZE AND POWER

Assuming a population clinical cure rate of 70% for standard IV therapy and 72.5% for telavancin, a total sample size of 210 (105 per treatment group) is deemed sufficient (80% power) to demonstrate noninferiority based on a noninferiority margin of 15% at a one sided significance level of 2.5%. This calculation does not take into account a potential stopping for futility at an interim analysis. With the futility analysis, the overall power of the study is approximately 64%.

A total of 248 subjects will be enrolled to allow for exclusion of up to 15% of subjects from the primary analysis set due to an LIE diagnosis or not meeting the mAT population criteria.

5 STUDY ENDPOINTS

All study endpoints and/or assessments include an evaluation type, ie, absolute value, change from baseline, an ADAM Type, either raw data or derived from raw data, ie, CRF or Lab-type data, an evaluation window, ie, screening ,Day 1, Days 1-85, and a summary type, ie, continuous, frequency, normal least squares.

5.1 General Endpoints

The following general endpoints will be summarized.

Table 2: Table of General Endpoints

Endpoint	Evaluation Type	ADaM Type	Reporting Window	Summary Type(s)
age	ABS	derived	D1-PD	C
age category by 65	CAT	derived	D1-PD	F
age category by 75	CAT	derived	D1-PD	F
sex	CAT	raw	D1-PD	F
ethnicity	CAT	raw	D1-PD	MF
race	CAT	raw	D1-PD	MF
height	ABS	raw	D1-PD	C
Actual weight	ABS	raw	D1-PD	C
Ideal body weight	ABS	raw	D1-PD	C
BMI	ABS	derived	D1-PD	C
Geographic region 1 (strata)	CAT	raw	D1-PD	MF
Geographic region 2 (US, Ex-US)	CAT	raw	D1-PD	F
Diabetes mellitus from CRF	CAT	raw	D1-PD	F
Diabetes mellitus from medical history	CAT	raw	D1-PD	F
Diabetes mellitus from CRF or medical history	CAT	raw	D1-PD	F
History of injection drug use w/in last 2 years	CAT	raw	D1-PD	F
Previous history of infective endocarditis w/in last 2 years	CAT	raw	D1-PD	F
HIV infection	CAT	raw	D1-PD	F
Hemodialysis	CAT	raw	D1-PD	F
Hepatitis C	CAT	raw	D1-PD	F
Liver Cirrhosis	CAT	raw	D1-PD	F
Malignancy requiring Chemo w/in last 2 years	CAT	raw	D1-PD	F

Endpoint	Evaluation Type	ADaM Type	Reporting Window	Summary Type(s)
Admission to hospital in previous 3 months	CAT	raw	D1-PD	F
Active immunosuppression	CAT	raw	D1-PD	F
Valvular heart disease	CAT	raw	D1-PD	F
Prosthetic cardiac devices	CAT	raw	D1-PD	F
Other non-cardiac prosthetic devices	CAT	raw	D1-PD	F
Creatinine Clearance using Ideal Body Weight, Central Lab	ABS	derived	D1-PD	C
Creatinine Clearance using Actual Body Weight, Central Lab	ABS	derived	D1-PD	C
Central echocardiogram parameters	ABS	Raw	D1-PD	C
Study disposition	ABS	raw	EOS	F
Reasons for study discontinuation	ABS	raw	EOS	text
Study drug disposition	ABS	raw	EOS	MF
Reasons for study drug discontinuation	ABS	raw	EOS	text
Days of therapy	ABS	derived	treatment	C
Primary infection type – IEAC adjudicated	CAT	raw	Day 1-8	MF
Safety Flag	CAT	Derived	NA	F
AT flag	CAT	Derived	NA	F
mAT flag	CAT	Derived	NA	F
mAT (UCB, CB, RIE)	CAT	Derived	NA	F
mAT (CB, RIE)	CAT	Derived	NA	F
mAT (UCB)	CAT	Derived	NA	F
mAT (CB)	CAT	Derived	NA	F
mAT (LIE)	CAT	Derived	NA	F
mAT (RIE)	CAT	Derived	NA	F
ME Flag	CAT	Derived	NA	F
ME (UCB, CB, RIE)	CAT	Derived	NA	F
ME (CB, RIE)	CAT	Derived	NA	F
ME (UCB)	CAT	Derived	NA	F
ME (CB)	CAT	Derived	NA	F
ME (LIE)	CAT	Derived	NA	F
ME (RIE)	CAT	Derived	NA	F

Note: D: day, CFB: change from baseline, ABS: absolute value or observed value; CAT: categorical/binary

Note: summary type, see Appendix 1:Reporting Structures for summary type abbreviations

5.2 Pathogen Endpoints

The following screening endpoints will be summarized.

Table 3: Table of Pathogen Endpoints

Endpoint	Evaluation Type	ADaM Type	Summary Type(s)
QBC collected (Y/N)	CAT	raw	F
Rapid diagnostic test type	CAT	raw	MF
QBC *S. aureus* type (MSSA, MRSA)	CAT	derived	MF
QBC status (no, mono, poly)	CAT	derived	MF
Post baseline *S. aureus* Status (mono, poly)	CAT	derived	MF
Type of S. aureus derived from central laboratory blood culture results (MSSA, MRSA)	CAT	derived	MF
Type of S. aureus identified by site in blood culture (MSSA, MRSA)	CAT	Derived	MF
Pathogens identified in baseline blood culture, site-reported	CAT	raw	MF
Vancomycin MIC (maximum)	ABS	derived	C
S. Aureus vancomycin MIC 1 (1 mg/L)	CAT	Derived	F
S. Aureus vancomycin MIC 2: (2 mg/L)	CAT	Derived	F
Clindamycin resistance	CAT	derived	F
Penicillin resistance	CAT	derived	F
S. aureus susceptibility to the study drug	CAT	derived	F

Note: D: day, CFB: change from baseline, ABS: absolute value or observed value; CAT: categorical/binary

Note: summary type, see Appendix 1: Reporting Structures for summary type abbreviations

5.3 Efficacy Endpoints

The following efficacy endpoints will be summarized (see Section 8.2 for definitions)

Table 4: Table of Efficacy Endpoints

Endpoint	Evaluation Type	ADaM Type	Reporting Window	Summary Type(s)
Clinical outcome at TOC – IEAC adjudicated	CAT	Raw	TOC	MF
Clinical response at EOT – IEAC adjudicated	CAT	Raw	EOT	MF
Development of new metastatic foci of S. aureus infection	CAT	Derived	Day 9 through end of study	MF
Time to initial clearance of *S. aureus* bacteremia	TTE	Derived	Day 1 through end of study	KM
28-day all-cause mortality	TTE	Derived	Treatment+28 days	KM
Clinical outcome at TOC – investigator-reported	CAT	Derived	TOC	MF
Clinical response at EOT – investigator-reported	CAT	Raw	EOT	MF

Note: D: day, CFB: change from baseline, ABS: absolute value or observed value; CAT: categorical/binary; TTE: time-to-event

Note: summary type, see Appendix 1: Reporting Structures for summary type abbreviations

5.4 Changes from Protocol-defined Efficacy Endpoints

5.4.1 Changes in the Categorization of Endpoints

The following endpoints were listed in the study protocol as key efficacy endpoints and are deemed safety endpoints in the Statistical analysis plan:

- Duration of treatment with study medication by baseline clinical diagnosis in the mAT and ME populations;
- Incidence of AEs, treatment-emergent AEs (TEAEs), SAEs, and deaths in the safety population;
- Incidence of key laboratory indices in the safety population.

5.4.2 Duration of Bacteremia Definition

Study Protocol describes the duration of bacteremia endpoint for subjects with a positive S. aureus blood culture on Day 1, as "the time (days) from randomization to all blood cultures negative for S. aureus for two successive days". This SAP changes the endpoint name and definition for the following reasons:

- to specify the pathogen of interest,
- to clarify that this is based on locally analyzed samples, because negative samples were not sent to the central lab,
- the reference date changed from randomization to the first dose of study drug, for consistency with other endpoints,
- the endpoint was defined for all subjects, for completeness,
- to indicate that time-to-event endpoint definition and analysis methods will be applicable,
- to limit the time when this endpoint is applicable to the initial treatment period, because after that the sampling may become sparse,
- to limit the time when this endpoint is applicable to the time prior to any treatment with a potentially effective non-study antibiotic (PENSAB),
- to specify censoring methodology for the subjects who did not achieve two consecutive blood negative blood cultures within the initial treatment period or those who received PENSABs.

5.4.3 Definition of All-cause 28-day Mortality

All-cause 28-day mortality was defined as all deaths that occur during the study, regardless of cause, on or before Day 28. The definition was modified to include deaths off study occurring on or before Day 28 and to specify time to event derivation and censoring methodology.

Furthermore, Study Protocol Section 3.4.3 states that 28-day all-cause mortality will be evaluated for subjects with a baseline diagnosis of CB or RIE in the mAT and ME populations. Exclusion of UCB subjects from the analysis population specified for this endpoint in the protocol is due to an oversight. The primary efficacy analysis population for this endpoint is the mAT (UCB, CB, and RIE).

5.5 Safety Endpoints

The following safety endpoints will be summarized (see Section 8.3 for definitions).

Table 5: Table of Safety Endpoints

Endpoint	Evaluation Type	ADaM Type	Reporting Window	Summary Type(s)
Study drug duration	ABS	Derived	Treatment	C
Number of days on Study Drug	ABS	Derived	Treatment	C
Per protocol study drug compliance	ABS	Derived	Treatment	C
On-treatment study drug compliance	ABS	Derived	Treatment	C
Prior Medication flag	ABS	Derived	Prior day 1	F
Concomitant medication flag	ABS	Derived	Treatment	F
Post study drug medication flag	ABS	Derived	Post EOT	F
Antibiotic medication flag	ABS	Derived	NA	F
Nephrotoxic Medication flag	ABS	Raw	NA	F
Renal adverse event flag	ABS	Raw	Treatment	F
Renal replacement therapy flag	ABS	Raw	Treatment	F
Clinical laboratory results (ie, hematology, serum chemistry, and urinalysis)	ABS	Raw	Treatment	C
Creatinine clearance: Day 2, 4, 8, 15, 22, 29, 36, and 43 on treatment	ABS	Derived	Treatment	C
Creatinine clearance: worst value on treatment through Day 8	ABS	Derived	Treatment	C
Creatinine clearance: worst value on-treatment at any time	ABS	Derived	Treatment	C
Creatinine clearance: last on treatment value	ABS	Derived	Treatment	C
Creatinine clearance: last value on study	ABS	Derived	Treatment	C

6 GENERAL ANALYSIS CONSIDERATIONS

6.1 Global Definitions and Conventions

All data from scheduled and unscheduled visits will be presented in the subject listings; however, unless noted otherwise, only data from scheduled visits will be included in the summaries, statistical analysis, and calculation of derived parameters.

6.2 Baseline Definition

For the derivation of baseline blood culture microbiology variables (Section 8.1.3), pre-dose blood cultures will be those collected before the first dose of study drug, but not more than 8 days before the 1st dose. The same will apply to variables based on central laboratory non-blood culture results. For derivation of baseline non-blood culture variables based on local laboratory results, sample collection time is not always available, and therefore samples collected on or prior Study Day 1 will be considered pre-dose.

For central laboratory safety measurements, vital signs, and ECG, baseline will be defined as the last (most recent) value before the first dose of study drug.

For temperature measurements, collection time was not always available, therefore baseline will be the latest (most recent) measurement of those either collected prior to Study Day 1 or collected on Day 1 within the nominal Screening visit.

6.3 Analysis Windows

All assessments will be summarized using analysis windows. The terminology of unscheduled will be applied to assessments that are outside an analysis window regardless of the nominal label associated with the assessments in the EDC system.

All data (scheduled and unscheduled visits) will be presented in the subject listings; however, unless noted otherwise, only data from assessments within analysis windows will be included in the summaries, statistical analysis, and calculation of derived parameters.

Selection of Data in the Event of Multiple Records in an Analysis Window

In general, if multiple, valid, non-missing observations exist at a visit or collection time point then records will be chosen based on the following:

- The record closest to the nominal time point in question, or,
- The later record if the two visits are equidistant from the time point, or,
- The average (arithmetic mean) if there is more than one record at the time point (generally applies to assessments done in triplicate).

The following visit windows will be used in the summary of clinical data.

Table 6: Visit Analysis Windows

Nominal Visit	Nominal Day	Start	Stop
Screening/ Baseline	≤ 1	See Section 6.2	Time of 1st dose of study drug
Days 1-4	1-4.	Time of 1st dose of study drug	Day 4
Week 1	8	Day 5	Day 11
Week 2	15	Day 12	Day 18
Week 3	22	Day 19	Day 25
Week 4	29	Day 26	Day 32
Week 5	36	Day 33	Day 39
Week 6	43	Day 40	Day 46
Week 7	50	Day 47	Day 53
Week 8	57	Day 54	Day 60

Efficacy Endpoints with Unique Windows

The following windows will be used for the clinical outcome at TOC and clinical response at EOT endpoints, both IEAC adjudicated and investigator-reported.

Table 7: Analysis Windows for Efficacy Endpoints

Visit	Protocol Version	Subject Classification	Nominal Day	Start	Stop
EOT/ Post Treatment	Any	Any	Day of last dose of study drug	Day of last dose of study drug	TOC
TOC/ EOS	Original/ Amendment 1	Assigned 4 weeks of treatment	Day 57	Day 54	Day 64
		Assigned 6 weeks of treatment	Day 71	Day 68	Day 78
	Amendment 2	UCB	Day 43	Day 40	Day 50
		CB	Day 57	Day 54	Day 64
		LIE/RIE	Day 71	Day 68	Day 78
	Amendment 3	UCB	Day 39	Day 36	Day 46
		CB/LIE/RIE	Day 53	Day 50	Day 60

EOS = end of study; EOT = end of treatment; TOC = test of cure

Safety Endpoints

The following windows summarize the definition of analysis windows applicable specifically to safety endpoints (defined in Section 8.3).

Table 8: Analysis Windows for Safety Endpoints

Window	Start	Stop
Adverse events	Sign of ICF	Maximum of follow-up visit or last contact
Treatment-emergent Adverse events, ECGs and abnormal safety laboratory values	First dose of study drug	Last dose + 28 days
On treatment creatinine clearance assessments	First dose of study drug	Last dose + 3 days
Medications post study drug medications	Medication start time after last dose of study drug + 24 hours	N/A
Medications prior to study drug	N/A	Medication end time prior to first dose of study drug
Medications concomitant with study drug	Post first dose, ie medication end time not prior to first dose of study drug	Last dose + 24 hours, ie medication start time is not after last dose + 24 hours
Systemic antimicrobial therapy starting prior to the first dose of study drug	Medication start time before 1st dose of study drug	N/A

Window	Start	Stop
Systemic antimicrobial therapy administered after Day 1	N/A	Medication end time is Day 2 or later or ongoing
Systemic antimicrobial therapy administered upon study drug discontinuation	Medication start day the same as the last dose of study drug or later	N/A
Day 2[a]	Time of 1st dose of study drug	Day 2
Day 4[a]	Day 3	Day 4
EOT[b]	Time of last dose of study drug	Time of last dose of study drug + 7 days
TOC/EOS[c]	Time of last dose of study drug + 8 days	Day of study completion or discontinuation

EOT = end of treatment; EOS = end of study; TOC = test of cure

a The visit window applies to Creatinine and Creatinine clearance samples only. In case of multiple non-missing observations in the time window, the record closest to the nominal time point (Day 2 or Day 4) will be selected

b In case of multiple non-missing observations in the time window, the earliest record will be selected.

c In case of multiple non-missing observations in the time window, the latest record will be selected

6.4 Evaluable Efficacy Assessment

Clinical response at EOT and clinical outcome at TOC endpoints, both investigator-reported and adjudicated, could only be considered evaluable, if they fall within the corresponding analysis windows (EOT or TOC).

All on-study assessments of development of new metastatic foci of S. aureus infection after Day 8 will be considered evaluable.

Blood cultures for determination of time to initial clearance of bacteremia collected after administration of potentially effective non-study antibiotics (as defined in Section 8.3.3) on or after Day 2 would be considered non-evaluable.

Death after study discontinuation but prior to Study Day 28 will be included in the derivation of the 28-day all-cause mortality endpoint.

6.5 Missing Data

In general, it is not anticipated that there will be considerable missing data. In general, missing data will not be imputed. Missing data for the following specific endpoints will be handled as follows:

Primary Efficacy Endpoint

Estimates of the clinical cure rate at TOC will be calculated relative to the number of subjects in the applicable analysis population. For example, any patient in the analysis population with an "indeterminate" or missing value for clinical outcome will be counted in both the numerator (as "failure") and denominator when calculating clinical cure rate.

Time to Initial Clearance of S. aureus bacteremia

Missing data for time to initial clearance of S. aureus bacteremia will be censored.

Twenty-eight Day All-Cause Mortality

Missing data for 28-day all-cause mortality will be censored.

Adverse Events

For graded adverse event summaries, subjects with an AE and no grade on the CRF will be graded as severe.

Missing dates/time for Adverse Events and Concomitant Medications

Missing dates will be handled as follows:

- Complete missing start date will be imputed as the same as first dose date;
- Partial missing start date imputation:
  - Missing start day with same month as first dose: minimum day (1, first dose day);
  - Missing start day with different month as first dose: 1
  - Missing start month with same year as first dose: minimum (January, first dose month);
  - Missing start month with different year as first dose: January
- Complete missing stop date will be considered as ongoing and not imputed;
- Partial missing stop date imputation:
  - Missing stop day: last day of month;
  - Missing stop month with same year as last dose: minimum (December, last dose month);
  - Missing stop month with different year as last dose: December

Missing times will be handled as follows:

- If a start or stop time is missing, the start time is imputed as 1 minute after a.m. midnight (00:01) and stop time is imputed to be 1 min before p.m. midnight (23:59).

Laboratory Data

For non-efficacy laboratory data, a missing baseline value will be replaced with the last available assessment, generally the screening assessment. A retest value will be used if the first test is invalidated, eg, specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of "< x" (x is considered as the LOD). More specifically, x−1 is used for data summarization if the data are reported in the form of "< x"; and x.e where e = d−1, will be used for analysis if the data are reported in the form of "< x.d";

- The LOD will be used for calculation of descriptive statistics if the data is reported in the form of "≤x" or "≥x.

6.6 Adverse Events

Recorded adverse events will be mapped according to the MedDRA thesaurus by the data management CRO for this study, with Theravance review and approval of the mappings. MedDRA, version 18.1 will be used.

6.7 Medications

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) by the data management CRO for this study with Theravance review and approval of the mappings. The CRO will use the September 2015 version of the WHODD.

6.8 Medical History

Medical history will be mapped according to MedDRA version 18.1.

6.9 General Considerations for Summaries

Analyses and tabulations will generally be prepared using SAS®, version 9.4 or later.

Presenting Multiple Summaries on Same Table Summary

In summary tables where multiple single line frequency summaries are being presented, the "n line" can be suppressed in the individual summaries and presented at the top of the summary a single time.

Ordering of Treatment Headers in Summary Tables

In summary tables, treatment headers will be presented in the following order:

- Standard Intravenous Therapy,
- telavancin,
- Total (Applicable to General Analysis and Exposure summaries).

Rounding

In general, the convention for rounding percentages is as follows:

- Values greater than or equal to x.x5 are rounded up,
- Values between 0 and less than x.x5 are rounded down,
- Values between –x.x5 and 0 are rounded up,
- Values less than or equal to –x.x5 are rounded down.

Significant Digits

Raw measurements will be reported the same as the data captured electronically or on the CRFs. Exceptions will be made for values reported with greater than 4 significant digits (round to 4 significant digits using a similar criterion as for percentages with the 5 in the last digit).

The following significant digit convention will be used for the purposes of summarizing data:

- Mean, median: 2 significant digits,
- Standard deviation: 3 significant digits,
- Minimum, maximum: 2 significant digits,
- Percentages: 1 decimal place.

6.10 Tables, Figures and Listings (TFLs)

A line listing of Tables, listings, and figures to be generated are in Appendix 6, respectively. Selected table, listing or figure mock-ups will be in a separate document.

7 ANALYSIS SETS

7.1 All-Treated Population

The All-Treated (AT) analysis population will include all subjects who

(1) Were randomized into the study after protocol Amendment 1 (that is, excluding any subjects enrolled under the original protocol).

(2) Received at least one dose of study drug (telavancin or standard intravenous therapy),

(3) Were classified according to the infection type (UCB, CB, RIE, or LIE),

Treatment assignment will be based on the treatment randomized. Subjects excluded from the AT population will be excluded from all efficacy data summaries and analyses.

Note: One subject enrolled under the original protocol will be excluded, because the subject was randomized to a higher dose of telavancin than the rest of the subjects. Another subject was discontinued from the study drug and the study prior to sufficient assessments to determine the infection type.

7.2 Microbiological All-Treated (mAT) Population

The Microbiological All-Treated (mAT) analysis population will include all subjects in the AT population who have a mono-microbial QBC positive for S. aureus. The mono-microbial status will be defined by the local and central microbiology laboratory analysis of baseline blood samples as presence of S. aureus in at least one such sample and no other pathogens in any of those samples (see Section 8.1 for details).

Reasons for exclusion from the mAT population will be summarized using the following categories: “Randomized but Not Treated”; “Enrolled prior to Amendment 1”, “Infection Type not Classified”, “No QBC Positive for S. aureus”; “Poly-microbial QBC”.

Treatment assignment will be based on randomized treatment.

7.2.1 Subpopulations of MAT Population According to Primary Infection Type

Efficacy summary and analyses will be performed within the subpopulations of the mAT population based on the IEAC-adjudicated primary infection type:

- mAT (UCB, CB, RIE),
- mAT (CB, RIE),
- mAT (UCB),
- mAT (CB),
- mAT (LIE),
- mAT (RIE).

7.3 Microbiological Evaluable (ME) Population

The Microbiological Evaluable (ME) population will include all subjects in the mAT population who meet the following criteria:

- Treatment compliance of ≥80% of prescribed study medication for their baseline diagnosis,
- Did not miss more than 2 consecutive doses of study medication,
- Completed the TOC visit within the window defined in Table 7,
- Did not have any recorded major protocol deviations,
- If assessed as failure at TOC, received at least 2 days of study medication,
- If assessed as cure at TOC, received at least 5 days of study medication,
- Did not receive any prohibited concomitant, potentially effective antibiotic.

Treatment assignment will be based on randomized treatment.

7.3.1 Subpopulations of ME Population According to Primary Infection Type

Exploratory efficacy summary and analyses may be performed within the subpopulations based on the IEAC-adjudicated primary infection type:

- ME (UCB, CB, RIE),
- ME (CB, RIE),
- ME (UCB),
- ME (CB),
- ME (LIE),
- ME (RIE).

7.4 Safety

The Safety analysis set will include all subjects who

(1) Were randomized into the study, and,

(2) Received at least one dose of study drug (telavancin or standard intravenous therapy).

Treatment assignment will be based on actual treatment. The Safety analysis set is the primary analysis set for safety analyses.

7.5 Strata and Covariates

At randomization, subjects will be stratified by geographic region:

- [a] United States, [b] Europe-1 (Germany, Italy, Latvia, Spain), [c] Europe-2 (Czech Republic, Georgia, Hungary, Poland, Romania), [d] South America (Argentina, Brazil, Colombia, Mexico, Peru).

Due the low enrollment outside of the US (strata b-d), the analysis will not be stratified by geographic region.

7.6 Examination of Subgroups

The following baseline subgroups are pre-defined:

- Age: [a] < 65 years; [b] ≥ 65 years;
- Age: [a] < 75 years; [b] ≥ 75 years;
- Gender: [a] male; [b] female;
- Geographic region: [a] US, [b] non-US;
- Type of S. aureus derived from central lab results: [a] MSSA; [b] MRSA;
- *S. Aureus* vancomycin MIC: [a] ≤ 1 mg/L; [b] > 1 mg/L;
- *S. Aureus* vancomycin MIC: [a] ≤ 2 mg/L; [b] > 2 mg/L;
- Baseline modified APACHE II score: [a] ≤ 15 points ; [b] > 15 points;
- Medical history of diabetes mellitus: [a] No; [b] Yes;
- Creatinine clearance categories: [a] > 50 mL/min; [b] ≤ 50 mL/min.

Selected analysis will be conducted using the subgroup analysis sets.

7.7 Inclusion and Exclusion Deviations

Deviations to inclusion and exclusion criteria will be identified prior to database lock and we be summarized in a listing with the deviation and the protocol version associated with the deviation.

7.8 Major Analysis Protocol Deviations

Major analysis protocol deviations that could potentially affect the conclusions of the study will be identified prior to database lock. Major analysis protocol deviations are defined as follows:

- Randomized subjects who did not satisfy efficacy inclusion (Amendment 4: 3,4,5) and exclusion criteria (Amendment 4: 1,2,3,4,8)
- Randomized subjects for whom pre-dose S. aureus sample was collected more than 7 days prior to 1st dose of study drug
- Subjects who received the wrong treatment,
- Subjects who received an excluded concomitant treatment or medication,
- Subjects who are less than 80% compliant with study medication,
- Subjects who are out of window for the primary efficacy assessment.

Subjects with major analysis protocol deviations will be identified before the database lock and provided in a listing.

In addition, a listing of all major deviations will be provided whether they impact analysis.

8 DEFINITION OF ANALYSIS VARIABLES

8.1 Demographic and Baseline Characteristics

8.1.1 Demographics

Age

Age will be calculated as of the date of informed consent form (ICF) and truncated to its integer value. The following formula is used:

$$age = floor\left(\frac{ICF\ Signing - Date\ of\ Birth}{365.25}\right)$$

In demographic data summaries, age will be characterized as < 65 years, 65 to < 75 years, and ≥ 75 years.

Geographic region

United States, Europe 1 (Germany, Italy, Latvia, Spain), Europe 2 (Czech Republic, Georgia, Hungary, Poland, Romania), South America (Argentina, Brazil, Colombia, Mexico, Peru).

8.1.2 Clinical Characteristics

BMI

BMI will be calculated and converted to metric units by the following:

$$BMI\left(kg/m^2\right)=\frac{weight\left(kg\right)}{height\left(m\right)^2}.$$

Ideal body weight (IBW)

Males:

$$\boldsymbol{IBW(kg)=50.0+0.9(height-152.0)}$$

Females:

$$\boldsymbol{IBW(kg)=45.5+0.9(height-152.0)}$$

For both males and females, if actual weight < ideal, then actual is ideal.

Creatinine clearance using ideal body weight

$$\boldsymbol{CrCL(mL/min)=\frac{(140-age)(IBW)}{(CreatBL)72}}$$

For females, multiply by 0.85.

Serum creatinine must be in mg/dL: mg/dL= umol/L * 0.0113.

Subjects on hemodialysis or subjects with renal replacement will not have a baseline CrCL calculated and will be excluded from mean summaries.

8.1.3 Disease-specific Clinical Characteristics

Qualifying blood culture (QBC) S. aureus status

The QBC status will be defined by the local and/or central microbiology laboratory analysis of pre-dose blood culture samples.

QBC positive for *S. aureus*: if S. aureus (reported as “MRSA”, “MSSA”, or “Staphylococcus aureus”) is detected in at least one pre-dose local or central microbiology blood culture.

QBC positive for mono-microbial *S. aureus*: if there are no other pathogens in any pre-dose local or central microbiology blood culture samples.

QBC positive for poly-microbial *S. aureus*: if additional pathogens other than *S. aureus* are detected in pre-dose blood cultures

QBC status will be defined as follows:

- “No QBC positive for *S. aureus*”,
- “Mono-microbial QBC positive for *S. aureus*”,
- “Poly-microbial QBC positive for *S. aureus*”.

Post baseline S. aureus status

The post baseline *S. aureus* status will be defined by the local and/or central microbiology laboratory analysis of post-dose blood culture samples.

Positive for mono-microbial *S. aureus*: if there are no other pathogens in any post-dose local or central microbiology blood culture samples.

Positive for poly-microbial *S. aureus*: if additional pathogens other than *S. aureus* are detected in post-dose blood cultures

QBC status will be defined as follows:

- “Mono-microbial post dose positive for *S. aureus*”,
- “Poly-microbial post dose positive for *S. aureus*”.

Type of S. aureus derived from central laboratory blood culture results

Subjects with at least one pre-dose centrally analyzed blood culture with S. aureus resistant to oxacillin are classified as having MRSA.

All other subjects with at least one pre-dose centrally analyzed blood culture positive for S. aureus are classified as having MSSA.

Blood culture *S. aureus* vancomycin minimal inhibitory concentration (MIC) (mg/L)

Vancomycin MIC will be defined as the highest *S. aureus* vancomycin MIC value of all pre-dose centrally analyzed blood cultures for the subject.

Blood culture *S. aureus* clindamycin resistance

Subjects with at least one pre-dose centrally analyzed blood culture with S. aureus resistant to clindamycin are classified as being resistant to clindamycin.

All other subjects with at least one pre-dose centrally analyzed blood culture positive for S. aureus are classified as susceptible to clindamycin.

Blood culture *S. aureus* penicillin resistance

Subjects with at least one pre-dose centrally analyzed blood culture with S. aureus resistant to penicillin are classified as being resistant to penicillin. All other subjects with at least one pre-dose centrally analyzed blood culture positive for S. aureus are classified as susceptible to penicillin.

Blood culture *S. aureus* other antibiotic MIC and susceptibility

Blood culture MIC (mg/dL) and, when possible, susceptibility to the following antibiotics was routinely assessed by the central microbiology lab:

- Ampicillin
- Cefazolin
- Cefoxitin
- Ceftaroline
- Clindamycin
- Daptomycin
- Erythromycin

- Linezolid
- Oxacillin
- Penicillin
- Telavancin
- Trimethoprim/sulfamethoxazole
- Vancomycin

If needed, baseline resistance or baseline MIC may be derived for these antibiotics as outlined above for clindamycin or vancomycin.

Blood culture *S. aureus* susceptibility to the study drug

Baseline *S. aureus* blood culture will be considered "Nonsusceptible" (for daptomycin) or "Resistant" (for other treatments) to the study drug, if at least one pre-dose centrally analyzed blood culture for the subject is nonsusceptible or resistant to the initial study drug. If there is at least one pre-dose S. aureus sample, and all pre-dose samples are susceptible to the study drug, then baseline S. aureus blood culture will be considered "Susceptible".

Pathogens derived from local laboratory blood culture results

Subjects with at least one pre-dose locally analyzed MRSA blood culture are classified as having MRSA.

All other subjects with at least one pre-dose locally analyzed blood culture positive for MSSA are classified as having MSSA.

Non-*S. aureus* pathogens identified by the local laboratory in pre-dose blood cultures will be summarized within the following categories:

- Gram-positive pathogens are the pathogens with genus or species names containing any of the following (not case sensitive): "Enterococcus", "Propionibacterium", "Staph", "Staphylococcus", "Strep", "Streptococcus".

- Gram negative pathogens are the pathogens with genus or species names containing any of the following (not case sensitive): "Acinetobacter", "Enterobacter", "Escherichia", "Proteus", "Pseudomonas", "Serratia", "Sphingomonas".

- Other pathogens are those that are not classified as gram-negative or gram-positive.

Type of S. aureus derived from central laboratory urine culture results

Subjects with at least one pre-dose centrally analyzed urine culture with *S. aureus* resistant to oxacillin are classified as having MRSA.

All other subjects with at least one pre-dose centrally analyzed urine culture positive for S. aureus are classified as having MSSA.

Pathogens derived from local laboratory urine culture results

Subjects with at least one pre-dose locally analyzed MRSA urine culture are classified as having “MRSA positive urine culture”.

All other subjects with at least one pre-dose locally analyzed urine culture positive for MSSA are classified as having “MSSA positive urine culture”.

Subjects who have at least one pre-dose locally analyzed urine culture sample, but no such samples positive for *S. aureus* will be classified as “No *S. aureus* in urine culture”. Subjects who don’t have any pre-dose locally analyzed urine culture samples will be classified as “Missing urine culture”.

Non-S. aureus pathogens identified by the local laboratory in pre-dose urine culture will be summarized.

8.2 Efficacy Variables

Clinical outcome at TOC

Clinical cure rate, defined as proportion of subjects with the clinical outcome of success, at TOC will be evaluated. The primary efficacy endpoint will be adjudicated by the IEAC blinded to treatment assignments.

Subjects with IEAC-adjudicated failure at EOT will be classified as having failure at TOC, regardless of the classification at TOC reported on the adjudication eCRF.

Clinical Response at EOT

Clinical response rate at EOT will be defined as the proportion of subjects with the clinical response of success at EOT.

Clinical outcome at TOC and clinical response at EOT (success, failure, indeterminate, or missing) will be summarized categorically.

Time to Initial Clearance of *S. aureus* Bacteremia

Clearance of *S. aureus* bacteremia is defined as occurring on the first date of all blood cultures negative for *S. aureus* for two successive days (need not be consecutive calendar days) after the first dose of study drug, in absence of PENSABs administered after Study Day 1 (defined in Section 8.3.3). This determination is based on locally analyzed blood cultures.

Time to initial clearance of S. aureus bacteremia will be defined, based on locally analyzed blood cultures, as (date of *S. aureus* bacteremia clearance) minus (date of the first dose of study drug) + 1, where the date of clearance is on Study Day 7 or earlier.

Subjects without any blood cultures between the first dose of study drug and Day 8, inclusively, will be censored at Day 1.

Subjects with at least one blood culture between the first dose of study drug and Day 8, inclusively, but without clearance of *S. aureus* bacteremia during that time will be censored at the last day a blood culture was collected on or before Day 8 or the day of the first PENSAB after Day 1, whichever is the earlier.

Development of New Metastatic Foci of S. aureus Infection

Development of new metastatic foci of S. aureus infection, defined as the development of new signs or symptoms consistent with S. aureus infection, will be assessed after Day 8 through the end of study (Yes, No, or missing) and summarized categorically.

28-day All-cause Mortality

Twenty-eight-day all-cause mortality is based on all deaths that occur on or before Day 28, irrespective of the cause. Deaths are defined as adverse events with fatal outcome reported on the AE eCRF; the date of death is the AE end date. Deaths on study (fatal AE end date is the same as the date of the end of study participation) and deaths off study (fatal AE end date after the end of study participation) will be included, as long as they occur on or before Day 28.

Twenty-eight-day all-cause mortality is a time-to-event endpoint defined, for the subjects who died on or before Day 28, as (date of death) minus (date of the first dose of study drug) + 1. Subjects without fatal adverse events and subjects who died after Day 28 will be censored at the earlier of Day 28 and the Study Day of study discontinuation.

For sensitivity analyses, 28-day on-study all-cause mortality may be defined similarly, based only on deaths on study.

Investigator Assessment of Clinical Outcome at TOC and Clinical Response at EOT

Investigator assessment of clinical outcome at TOC and investigator assessment of clinical response at EOT will be derived for each subject using the data reported by the investigator on eCRF.

Clinical response at EOT will be success, failure, indeterminate, or missing, as reported.

Clinical outcome at TOC will be clinical success, failure, indeterminate, or missing as reported, except subjects with clinical response = failure at EOT will be considered as having failure at TOC regardless of the assessment reported on eCRF.

8.3 Safety Variables

The list of safety variables is provided in Section 5.5.

8.3.1 Adverse Events

Adverse events (AEs) are recorded from signing of the informed consent form through the final follow-up assessment. Unless otherwise specified, only treatment-emergent AEs will be summarized in the tables. Treatment-emergent AEs are defined as AEs with an onset date on or after the initiation of the first study drug up to the last day of study drug plus 28 days or the date of study completion or discontinuation, whichever is the earlier.

Renal adverse events are those coded to the renal and urinary disorders system organ class.

8.3.2 Prior and Concomitant Medications

Prior and concomitant antimicrobial therapy will be collected on a dedicated eCRF throughout the subject's study participation. Other prior and concomitant medications will be collected on another eCRF.

Nephrotoxic medications will be identified by the Medical Monitor review of the list of WHODD coded preferred drug names and routes of administration of the concomitant antimicrobial therapy and other medications. The final medical review identifying nephrotoxic medications will occur after all subject data have been reviewed, verified, and soft locked and prior to the data base lock (Appendix 2).

For the purposes of safety data reporting, the medications will be classified as prior to, concomitant with, or post study drug (mutually exclusive categories) as described in Table 8.

8.3.3 Systemic Antimicrobial Therapy

8.3.3.1 Potentially Effective Non-study Antibiotic (PENSAB) Definition

Potentially effective non-study antibiotics (PENSABs) will be defined using a two-tier review of antimicrobial therapy by a Study Medical Monitor. The final medical review identifying PENSABs will occur after all subject data have been reviewed, verified, and soft locked and prior to the data base lock.

First, the list of WHODD coded preferred drug names and routes of administration of the concomitant antimicrobial therapy will be reviewed, and the medications will be classified as:

- MRSA coverage: yes/no/possible
- MSSA coverage: yes/no/possible
- Systemic therapy: yes/no

This information will be merged with the subject type of S. aureus derived from central laboratory blood culture results.

The following medications will be considered not PENSABs:

- Those classified as Systemic therapy = “no”
- In subjects with MRSA, medications with potential MRSA coverage = “no”
- In subjects with MSSA, medications with potential MSSA coverage = “no”

The following systemic therapy will be considered PENSABs:

- In subjects with MRSA, medications with potential MRSA coverage = “yes”
- In subjects with MSSA, medications with potential MSSA coverage = “yes”

Second, for the subjects with systemic coverage and the medications with “possible” coverage of the subject’s *S. aureus* type (MRSA or MSSA), the medication will be flagged as “possible” PENSAB, and additional subject level information will be reviewed to determine whether the medication is a PENSAB, for instance: how long the medication was administered for; medication indication; baseline clindamycin or penicillin resistance (if the medication is clindamycin or penicillin); antibiotic susceptibility of the centrally analyzed S. aureus blood and other cultures.

8.3.3.2 Systemic Antimicrobial Therapy Timing

For the purposes of assessing impact on efficacy evaluation, systemic antimicrobial therapy will be classified by:

- Whether or not the medication started prior to the first dose of study drug (yes/no);
- Whether or not the medication was administered at any time after Study Day 1 as described in Table 8 (yes/no);
- Whether or not the medication started upon study drug discontinuation (yes/no);

Note that a medication administered after the first dose of study drug could have also started prior to the first dose or upon study drug discontinuation.

For the systemic antimicrobial therapy starting prior to the first dose of study drug, the number of hours from the start of medication to the first dose of study drug will be computed. For the purposes of this calculation, if the start time of the medication is unknown, it will be imputed as 00:01 on the day of the medication start. If the start date is unknown, it will be imputed with the 1st of the month; if the start month is unknown, it will be imputed with January. The number of hours derived based on imputed values will be flagged.

9 ANALYSES

Table, figures and listing titles are denoted in underlined text.

9.1 General Analyses

9.1.1 Analysis Sets

Analysis populations will be summarized by counts and percentages as follows:

- **All Randomized**, n
- **Safety**, n
- **All (AT)**, n [100%]
- **Microbiological All Treated (mAT)**, n [% of AT]
- mAT (UCB, CB, RIE), n [% of AT] (% of mAT)
- mAT (CB, RIE), n [% of AT] (% of mAT)
- mAT (UCB), n [% of AT] (% of mAT)
- mAT (CB), n [% of AT] (% of mAT)
- mAT (LIE), n [% of AT] (% of mAT)
- mAT (RIE), n [% of AT] (% of mAT)
- **Microbiological Evaluable (ME)**, n [% of AT] (% of mAT)
- ME (UCB, CB, RIE), n [% of AT] (% of mAT) [[% of ME]]
- ME (CB, RIE), n [% of AT] (% of mAT) [[% of ME]]
- ME (UCB), n [% of AT] (% of mAT) [[% of ME]]
- ME (CB), n [% of AT] (% of mAT) [[% of ME]]
- ME (LIE), n [% of AT] (% of mAT) [[% of ME]]
- ME (RIE), n [% of AT] (% of mAT) [[% of ME]].

9.1.2 Subject Disposition

Subject disposition information will be summarized for all subjects by dose. The summary will include:

- Number of randomized subjects,
- Number and percentage of subjects randomized and treated with study drug (AT),
- Number and percentage of subjects completing the study,
- Number and percentage of subjects by reason discontinuing the study
    - Completed
    - Lost to follow-up
    - Withdrawal by subject
    - Death
    - Other
- Number and percentage of subjects completing the study drug,
- Number and percentage of subjects by reason discontinuing the study drug
    - Subjects completed dosing regimen
    - Adverse Event
    - Withdrawal by subject
    - Lost to follow-up
    - Physician decision
    - Pregnancy
    - Protocol violation
    - Study terminated by Sponsor
    - Death
    - Other

A listing of subject disposition will include the AT analysis set status, the initial date of informed consent signed, the date of first dose and last dose of study drug, primary category for subject discontinuation of study medication, the date of last visit, study completion status, primary category for study termination, and the date of last contact.

In addition, all subjects with a discontinuation or disposition category of (1) Other, (2) physician decision, or (3) Withdrawal by subject will include verbatim explanations in the listing

9.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics, age, sex, race, ethnicity, height, weight, and BMI) will be summarized for the AT analysis set.

A listing will also be provided.

9.1.4 Classification of Infection Type

Classification of infection type will be summarized as follows:

Investigator Assessments:

- Subjects in AT Population, n
    - Uncomplicated Bacteremia (UCB), n (%)
    - Complicated Bacteremia (CB), n (%)
    - Right-Sided Infective Endocarditis (RIE), n (%)
    - Left-Sided Infective Endocarditis (LIE), n (%)
    - Unknown (missing), n (%)
- Subjects in mAT Population, n
    - Uncomplicated Bacteremia (UCB), n (%)
    - Complicated Bacteremia (CB), n (%)
    - Right-Sided Infective Endocarditis (RIE), n (%)
    - Left-Sided Infective Endocarditis (LIE), n (%)
    - Unknown (missing), n (%)

Adjudicated Investigator Assessments:

- Subjects in AT Population, n
    - Uncomplicated Bacteremia (UCB), n (%)
    - Complicated Bacteremia (CB), n (%)
    - Right-Sided Infective Endocarditis (RIE), n (%)
    - Left-Sided Infective Endocarditis (LIE), n (%)
    - Unknown (missing), n (%)
    - Not adjudicated, n (%)
- Subjects in mAT Population, n
    - Uncomplicated Bacteremia (UCB), n (%)
    - Complicated Bacteremia (CB), n (%)
    - Right-Sided Infective Endocarditis (RIE), n (%)
    - Left-Sided Infective Endocarditis (LIE), n (%)

- Unknown (missing), n (%)
- Not adjudicated, n (%)

9.1.5 Clinical Characteristics at Baseline

Three summary of baseline clinical characteristics will be provided, one each for the AT, mAT and ME populations:

- Age Category
  - <65 years, n (%)
  - ≥65, <75 years, n (%)
  - ≥ 75 years, n (%)
- Creatinine clearance, based on ideal body weight (mL/min),
- Creatinine clearance, based on actual body weight (mL/min),
- Type of S. aureus identified by the site
  - MRSA, n (%)
  - MSSA, n (%)
  - Unknown (missing), n (%)
- Type of S. aureus derived from central lab results
  - MRSA, n (%)
  - MSSA, n (%)
  - Unknown (missing), n (%)
- Blood culture S. aureus Vancomycin MIC (mg/L)
  - ≤ 1 mg/L, n (%)
  - > 1 mg/L, n (%)
  - ≤ 2 mg/L, n (%)
  - > 2 mg/L, n (%)
- Blood culture S. aureus antibiotic resistance
  - clindamycin, n (%)
  - penicillin, n (%)

A listing will also be provided.

9.1.6 Select Medical History

A summary of select medical history will be provided using the AT and the mAT populations:

- Diabetes mellitus (from CRF or MH), n (%)
- History of injection drug use w/in last 2 years, n (%)
- Previous history of infective endocarditis w/in last 2 years, n (%)
- HIV infection, n (%)
- Hemodialysis, n (%)
- Hepatitis C, n (%)
- Liver Cirrhosis, n (%)
- Malignancy requiring Chemo w/in last 2 years, n (%)
- Admission to hospital in previous 3 months, n (%)
- Active immunosuppression, n (%)
- Valvular heart disease, n (%)
- Prosthetic cardiac devices, n (%)
- Other non-cardiac prosthetic devices, n (%)

9.1.7 Pathogens Isolated from Qualifying Blood Cultures

Three summaries of isolated pathogens will be provided. A summary of pathogens isolated from blood cultures by the site, a summary of pathogens isolated from blood cultures by Central lab and a summary of pathogens isolated from blood cultures by the Site OR Central lab will be provided as follows (by baseline and by post baseline):

Rapid diagnostic test for qualifying blood culture

- PNA-FSH, n (%)
- MALDI-TOF, n (%)
- Qualitative PCR, n (%)
- Multiplex microarray, n (%)
- Multiplex PCR, n (%)
- Other, n (%)
- Not applicable, n (%)

Baseline (qualifying blood culture)

- Number of subjects in the AT population, n (%)
- Number of subjects with confirmed pathogens isolated from blood cultures, n (%)
- Gram-positive pathogens, n (%) [by pathogen]

- Gram-negative pathogens, n (%) [by pathogen]
- Other, n (%) [by pathogen]

Post Baseline

- Number of subjects in the AT population, n (%)
- Number of subjects with confirmed pathogens isolated from blood cultures, n (%)
- Gram-positive pathogens, n (%) [by pathogen]
- Gram-negative pathogens, n (%) [by pathogen]
- Other, n (%) [by pathogen]

9.1.8 Signs and Symptoms of Bacteremia at Enrollment

A summary of signs and symptoms of bacteremia at enrollment will summarize the following:

- Subjects with at least one signs and symptom of bacteremia, n (%)
- Temperature ≥ 38.0^{o} C, n (%)
- White blood cell (WBC) count > 10,000 or < 4,000 cells/μL, or > 10% immature neutrophils (bands) regardless of total peripheral WBC count, n (%)
- Tachycardia (heart rate > 90 bpm), n (%)
- Tachypnea (respiratory rate >20 breaths/min), n (%)
- Hypotension (systolic blood pressure <90 mmHg), n (%)
- Signs and symptoms of localized catheter-related infection, n (%)

9.1.9 Characteristics of Bacteremia at Enrollment

A summary of the characteristics of bacteremia at enrollment will summarize the following:

- Subjects with complicated bacteremia with known metastatic foci of S. aureus infection, n (%)
- Endocarditis, n (%)
- Lung (Septic Pulmonary Emboli), n (%)
- Vein (Septic Thrombophlebitis), n (%)
- Epidural Abscess, n (%)
- Septic Arthritis (Joint), n (%)
- Renal Abscess, n (%)
- Splenic Abscess, n (%)
- Hepatic Abscess, n (%)
- Soft Tissue Abscess, n (%)

- Other Location, n (%)

In addition, a summary of risk factors for bacteremia will summarize the following:

- Subject with at least one risk factor for bacteremia, n (%)
- A Central Venous Catheter (CVC) in the Internal Jugular or Subclavian Vein, n (%)
- Any CVC Considered to be the Source of the Infection, n (%)
- Presence of a Long-term Intravascular Catheter, n (%)
- New or Diastolic Cardiac Murmur, n (%)
- Community Onset Bacteremia, n (%)
- Pathogen known to be MRSA at Enrollment, n (%)
- Duration of Symptoms >= 2 Days at Time of Presentation, n (%)
- Skin Exam Findings Suggesting Acute Systemic Infection, n (%)

9.1.10 Baseline modified APACHE II Scores

A summary of the Baseline modified APACHE II Scores and Components will summarize the following (see Appendix 4 for APACHE II Assessment Criteria details)

- Total Baseline modified APACHE II Score, calculated as the sum of A (Total Acute Physiology Score (APS points)) + B (Age points) + C (Chronic Health points),
- APS points (A)
- Age points (B)
- Chronic Health points (C)

Acute Physiology Score (APS) Variables

- Temperature – rectal (°C)
- Mean Arterial Pressure (mm Hg)
- Heart Rate
- Respiratory Rate (non-ventilated or ventilated)
- Oxygenation (mm Hg)
- Arterial pH
- Serum Sodium (mmol/l)
- Serum Potassium (mmol/l)
- Serum Creatinine (mg/dl, Double point score for acute renal failure)
- Hematocrit (%)
- White Blood Count (in 1000/mm3)
- Glasgow-Coma-Scale (GCS)

- Serum HCO3 (venous, mmol/l, use if no ABGs)

A listing will also be provided.

9.2 Efficacy Analyses

For all efficacy data analyses, the mAT (UCB, CB, and RIE) group will be used unless otherwise specified.

9.2.1 General Considerations for Efficacy Analyses

Analysis Set for Efficacy Analyses

For all efficacy data analyses, the mAT (UCB, CB, and RIE) analysis population will be used unless otherwise specified.

9.2.2 Primary Efficacy Evaluation: Adjudicated Clinical Outcome at TOC

Hypothesis

The primary estimate of interest, proportion of subjects with adjudicated clinical cure at end of treatment, is used to evaluate the effectiveness of telavancin therapy relative to standard intravenous therapy, as assessed through a non-inferiority margin of 15%, in all patients in the microbiological all treated population with a bacteremia type of uncomplicated bacteremia, complicated bacteremia and right-side infective endocarditis.

The following hypothesis testing schema will be employed to assess the primary endpoint: The null hypothesis is that telavancin is clinically inferior to standard therapy, where "clinically inferior" is defined as having a population clinical cure rate that is 15 percentage points (or more) lower than that for standard IV therapy. The alternative hypothesis is that telavancin is at least clinically noninferior to standard IV therapy, where "clinical noninferiority" is defined as having population clinical cure rates that differ by less than 15 percentage points. Expressed symbolically, the null hypothesis (H_0) and the alternative hypothesis (H_1) are as follows:

$$H_0: \pi_T - \pi_S \leq -15\%$$

$$H_1: \pi_T - \pi_S > -15\%,$$

where π_T and π_S denote the population clinical cure rates of telavancin and standard IV therapy, respectively.

A two-sided 95% confidence interval (CI) on the treatment difference, $\pi_T - \pi_S$, will be constructed.

If the lower confidence limit (CL_L) is less than or equal to -15%, then the null hypothesis of inferiority will not be rejected. If CL_L is greater than -15%, then the null hypothesis of clinical inferiority will be rejected in in favor of the alternative hypothesis of clinical noninferiority.

Analysis and Summary Tables

Adjudicated clinical outcome at TOC (cure, failure, indeterminate, or missing) will be summarized categorically. The proportion of subjects with clinical cure is the number of subjects with an adjudicated outcome of “cure” at TOC divided by the total number of subjects for each treatment group.

The point estimate and CI for the treatment difference will be calculated using the normal approximation to the binomial distribution without continuity correction. If any cell size is less than 10, the CI will be calculated using the method of Agresti and Caffo [1] to adjust for the sparse cell size.

A summary of adjudicated clinical outcome at TOC will include observed counts and proportions for each outcome and the corresponding point estimate for the difference of proportions and 95% CI.

9.2.3 Sensitivity Analyses of the Primary Endpoint

Sensitivity Analysis: Analysis Populations

A summary of adjudicated clinical outcome at TOC by analysis population will repeat the primary analysis on the following analysis populations summarizing only the "cure" counts, proportions, treatment difference and 95% CI for the following analysis populations:

- **All (AT)**,
- **Microbiological All Treated (mAT)**,
- mAT (UCB, CB, RIE)[primary]
- mAT (CB, RIE),
- mAT (UCB),
- mAT (CB),
- mAT (LIE),
- mAT (RIE),
- **Microbiological Evaluable (ME)**,
- ME (UCB, CB, RIE),
- ME (CB, RIE),
- ME (UCB),
- ME (CB),
- ME (LIE),
- ME (RIE).

Sensitivity Analysis: Subgroups

A summary of adjudicated clinical outcome at TOC by subgroups (mAT UCB, CB, and RIE) will repeat the primary analysis on the following analysis populations by subgroups summarizing only the "cure" counts and proportions, treatment difference and 95% CI for the following analysis populations:

- mAT (UCB, CB, RIE): < 65 years
- mAT (UCB, CB, RIE): ≥ 65 years
- mAT (UCB, CB, RIE): < 75 years
- mAT (UCB, CB, RIE): ≥ 75 years
- mAT (UCB, CB, RIE): male
- mAT (UCB, CB, RIE): female
- mAT (UCB, CB, RIE): US

- mAT (UCB, CB, RIE): ex-US
- mAT (UCB, CB, RIE): MSSA
- mAT (UCB, CB, RIE): MRSA
- mAT (UCB, CB, RIE): *S. Aureus* vancomycin MIC ≤ 1 mg/L
- mAT (UCB, CB, RIE): *S. Aureus* vancomycin MIC > 1 mg/L
- mAT (UCB, CB, RIE): *S. Aureus* vancomycin MIC ≤ 2 mg/L
- mAT (UCB, CB, RIE): *S. Aureus* vancomycin MIC > 2 mg/L
- mAT (UCB, CB, RIE): CrCL > 50 mL/min
- mAT (UCB, CB, RIE): CrCL ≤ 50 mL/min

A summary of adjudicated clinical outcome at TOC by subgroups (ME UCB, CB, and RIE) will repeat the primary analysis on the following analysis populations by subgroups summarizing only the “cure” counts, proportions, treatment difference and 95% CI for the following analysis populations:

- ME (UCB, CB, RIE): < 65 years
- ME (UCB, CB, RIE): ≥ 65 years
- ME (UCB, CB, RIE): < 75 years
- ME (UCB, CB, RIE): ≥ 75 years
- ME (UCB, CB, RIE): male
- ME (UCB, CB, RIE): female
- ME (UCB, CB, RIE): US
- ME (UCB, CB, RIE): ex-US
- ME (UCB, CB, RIE): MSSA
- ME (UCB, CB, RIE): MRSA
- ME (UCB, CB, RIE): *S. Aureus* vancomycin MIC ≤ 1 mg/L
- ME (UCB, CB, RIE): *S. Aureus* vancomycin MIC > 1 mg/L
- ME (UCB, CB, RIE): *S. Aureus* vancomycin MIC ≤ 2 mg/L
- ME (UCB, CB, RIE): *S. Aureus* vancomycin MIC > 2 mg/L
- ME (UCB, CB, RIE): CrCL > 50 mL/min
- ME (UCB, CB, RIE): CrCL ≤ 50 mL/min

9.2.4 Secondary Efficacy Evaluation: Adjudicated Clinical Response at EOT

Clinical response at EOT is handled in the similar manner as the clinical outcome at TOC.

Analysis and Summary Tables

Adjudicated Clinical response at EOT (cure, failure, indeterminate, or missing) will be summarized categorically. The proportion of subjects with clinical response is the number of subjects with an adjudicated outcome of "success" at EOT divided by the total number of subjects for each treatment group.

The point estimate and CI for the treatment difference will be calculated using the normal approximation to the binomial distribution without continuity correction. If any cell size is less than 10, the CI will be calculated using the method of Agresti and Caffo [1] to adjust for the sparse cell size.

A summary of adjudicated clinical response at EOT will include observed counts and proportions for each outcome and the corresponding point estimate for the difference of proportions and 95% CI.

A summary of adjudicated clinical response at EOT by analysis population will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the "success" counts and proportions, treatment difference and 95% CI for the following analysis populations.

A summary of adjudicated clinical response at EOT by subgroups (mAT UCB, CB, and RIE) will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the "success" counts and proportions, treatment difference and 95% CI for the following analysis populations.

A summary of adjudicated clinical response at EOT by subgroups (ME UCB, CB, and RIE) will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the "success" counts and proportions, treatment difference and 95% CI for the following analysis populations.

9.2.5 Secondary Efficacy Evaluation: Investigator Clinical Outcome at TOC

A summary of investigator clinical outcome at TOC will include observed counts and proportions for each outcome and the corresponding point estimate for the difference of proportions and 95% CI.

A summary of investigator clinical outcome at TOC by analysis population will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the “cure” counts and proportions, treatment difference and 95% CI for the following analysis populations.

A summary of investigator clinical outcome at TOC by subgroups (mAT UCB, CB, and RIE) will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the “cure” counts and proportions, treatment difference and 95% CI for the following analysis populations.

A summary of investigator clinical outcome at TOC by subgroups (ME UCB, CB, and RIE) will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the “cure” counts and proportions, treatment difference and 95% CI for the following analysis populations.

In addition, the Reasons for Failure or Indeterminate in Clinical Response at Test-of-Cure (Investigator-Assessed) will summarize the reasons for lack of response (Appendix 5).

9.2.6 Secondary Efficacy Evaluation: Investigator Clinical Response at EOT

A summary of investigator clinical response at EOT will include observed counts and proportions for each outcome and the corresponding point estimate for the difference of proportions and 95% CI.

A summary of investigator clinical response at EOT by analysis population will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the “success” counts and proportions, treatment difference and 95% CI for the following analysis populations.

A summary of investigator clinical response at EOT by subgroups (mAT UCB, CB, and RIE) will repeat the primary analysis on the same analysis populations as the corresponding

summary for the primary endpoint summarizing only the "success" counts and proportions, treatment difference and 95% CI for the following analysis populations.

A summary of investigator clinical response at EOT by subgroups (ME UCB, CB, and RIE) will repeat the primary analysis on the same analysis populations as the corresponding summary for the primary endpoint summarizing only the "success" counts and proportions, treatment difference and 95% CI for the following analysis populations.

In addition, the Reasons for Failure or Indeterminate in Clinical Response at EOT (Investigator-Assessed) will summarize the reasons for lack of response (Appendix 5).

9.2.7 Secondary Efficacy Evaluation: Time to initial clearance of *S. aureus* bacteremia

Analysis and Summary Tables

Time to event endpoints will be handled using Kaplan-Meier methodology. Subjects not experiencing the event in question up to and including the specified time period will be considered to be censored at the specified end of evaluation.

Sample code for the procedure in SAS is specified below:

```
proc lifetest data=data1;
time timeto*event(0);
strata trt01pn;
ods output    quartiles=medci(where=(percent=50))
              ProductLimitEstimates=estimate(keep=trt01pn timeto survival
                    stderr where=(survival>=0 and timeto>0.0))
              ProductLimitEstimates=atrisk(keep=trt01pn timeto failed left);
```

A summary of the time to initial clearance of *S. aureus* bacteremia will include the survival estimate and number at risk for each time point with an event, regardless if the event occurred within all treatment groups. Summaries will include up to the end of the maximum nominal evaluation period. Treatment groups not having an overlapping time will have the survival probability for the preceding time repeated until and event occurs within said treatment group. The cumulative number of events will be summarized.

The time to event reporting structure will be used to summarize the time to first event.

Nominal p-values will be reported.

Figures

Inverse Survival Plot

The Inverse Survival plot of the Kaplan-Meier estimates will be provided.

9.2.8 Secondary Efficacy Evaluation: 28-day all-cause mortality

Analysis and Summary Tables

Time to event endpoints will be handled using Kaplan-Meier methodology. Subjects not experiencing the event in question up to and including the specified time period will be considered to be censored at the specified end of evaluation.

A summary of the 28-day mortality will include the survival estimate and number at risk for each time point with an event, regardless if the event occurred within all treatment groups. Summaries will include up to the end of the maximum nominal evaluation period. Treatment groups not having an overlapping time will have the survival probability for the preceding time repeated until and event occurs within said treatment group. The cumulative number of events will be summarized.

The time to event reporting structure will be used to summarize the time to first event.

Nominal p-values will be reported.

Figures

Inverse Survival Plot

The Inverse Survival plot of the Kaplan-Meier estimates will be provided.

9.2.9 Multiplicity Adjustment

No adjustment for multiplicity is planned as all inferences are confidence interval based.

9.3 Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), and quantitative parameters from 12-lead ECGs. Vital signs will be summarized in terms of observed values and changes from baseline.

9.3.1 Extent of Exposure

Study drug exposure and compliance will summarize the number of days of study medication and to total duration of study treatment. Study drug duration will be defined based on the number of days within a given treatment period (date of last dose – date of first dose + 1).

- Actual number of days of study medication
- Duration of study treatment
- Compliance rate (%)

In addition, Study drug exposure and compliance by infection type will summarize the following exposure and compliance metrics will be summarized by infection type ([1] CB [2] LIE [3] RIE [4] UCB)

- Actual number of days of study medication
- Duration of study treatment
- Compliance rate (%)
- Compliance rate to protocol stated treatment duration (%)

Compliance rate is defined as:

- number of doses / treatment duration for a once daily IV therapy
- number of doses / (2*treatment duration) for a 2x daily IV therapy
- number of doses / (3*treatment duration) for a 3x daily IV therapy
- number of doses / (4*treatment duration) for a 4x daily IV therapy

Compliance rate to protocol stated treatment duration is defined as the minimum of compliance rate and:

- number of doses / minimum treatment duration for the infection type for a once daily IV therapy
- number of doses / (2* minimum treatment duration for the infection type) for a 2x daily IV therapy
- number of doses / (3* minimum treatment duration for the infection type) for a 3x daily IV therapy

- number of doses / (4* minimum treatment duration for the infection type) for a 4x daily IV therapy

9.3.2 Adverse Events

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term (PT) and severity and/or relatedness, the frequency and percentage of subjects reporting each observed event.

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject.

Subjects who experienced treatment-limiting AEs will be listed. Treatment-limiting AEs are defined as any event that leads to permanent or temporary discontinuation from treatment, or a reduction in the treatment dose.

Summary of adverse events will be dependent on adverse events observed. If no adverse events meeting a specific table are observed, the summary table will not be completed. Blank summary tables will not be utilized.

The following is the list of adverse event tables:

Overall:

- Overall Summary of Adverse Events

By preferred term:

- Treatment-emergent Adverse Events by SOC and PT
- Treatment-emergent Adverse Events by PT
- Treatment-emergent Adverse Events by SOC and PT occurring in more than 5% of Study population

By severity:

- Treatment-emergent Adverse Events by SOC, PT and Severity
- Moderate or Severe Treatment-emergent Adverse Events by SOC and PT
- Serious Adverse Events
- Deaths during or Post Study

By relatedness:

- Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-Related Treatment-emergent Adverse Events by SOC, PT and Severity
- Moderate or Severe Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-related Serious Adverse Events

Other:

- Adverse events leading to premature study drug discontinuation
- Adverse events leading to temporary interruption of study drug

The overall summary of adverse events will include the following summary lines, any AE, Moderate or severe AEs, Moderate or severe AEs related to Study Drug, Serious AEs, Serious AEs related to Study Drug, AEs leading to discontinuation, AEs leading to interruption, Deaths during Study.

9.3.2.1 Renal Adverse Events

A summary of Renal AE, by visit, will summarize the number and percentage of subjects with a renal AE in the renal and urinary SOC.
A listing of additional information collected for renal AEs will be provided.

9.3.3 Vital Signs

For each nominal time point, vital signs will be summarized in terms of observed values and changes from Baseline. Outlier values of vital signs will be flagged in the listing.

Table 9: Vital Signs Outlier Thresholds

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
<40 >110	<85 >160	<45 >100

9.3.4 ECG

A summary of ECG parameters, parameters reported separately QTcF, PR interval, QT interval, QRS duration, RR, and HR, will be summarized in terms of observed values and change from baseline.

Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (eg, denominator of the summary statistic) for that time point.

All recorded values by central reader at ECG core lab for the standard 12-lead electrocardiogram parameters will be presented in a by-subject listing.

Outlier Analysis

The number of subjects with absolute ECG values and change from baseline in the ranges shown in Table 10 will be presented in Electrocardiogram Outlier Summary by Visit and Time Point.

In addition in the same summary, QTcF will also be summarized by the following categories, Normal (males ≤430, females ≤450), Borderline (males (>430, ≤450); females (>450, ≤470)) and Prolonged (males >450, females >470).

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

Investigator Assessment of ECG Readings

The investigators' assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Table 10: ECG Test Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF change from Baseline (msec)
>120	>20	> 200	> 15	> 120	Males:	≤ 30
>130	>30	> 220	> 25		≤ 430	>30, ≤ 60
					> 430	> 60
					> 450	
					> 470	
					> 480	
					> 500	
					Females:	
					≤ 450	
					> 450	
					> 470	
					> 480	
					> 500	

9.3.5 Clinical Laboratory Results

Laboratory data, hematology, serum chemistry and urinalysis, will be summarized in terms of observed values, changes from baseline for each period. In addition, changes from baseline for each period relative to normal ranges (eg, shifts from normal to abnormal high/low) will be summarized in hematology: shift from baseline, serum chemistry: shift from baseline and urinalysis: shift from baseline.

Listings will flag laboratory values that are outside of normal range.

A listing of all abnormal lab values will be provided.

9.3.6 Medical History

Medical history collected at screening will be provided in a table and data listing.

9.3.7 Prior and Concomitant Medications

Prior, concomitant and post study drug medications will be listed and summarized separately. The following summaries will be provided:

- Prior Systemic Antimicrobials
- Concomitant Systemic Antimicrobials
- Post Study Drug Systemic Antimicrobials
- Nephrotoxic Medications Prior to Study Drug
- Concomitant Nephrotoxic Medications
- Post Study Drug Nephrotoxic Medications
- Prior Medications
- Concomitant Medications
- Post Study Drug Medications

10 REFERENCES

1. Agresti, A. and B. Caffo, Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. The American Statistician, 2000. **54**(4): p. 280-288.

Appendix 1: Reporting Structures for Data Summary

Reporting Structures

C: Continuous endpoints will be presented with an 8-point summary using the following reporting structure, unless otherwise noted,

N	x
Mean (SD)	x.xx (x.xx)
Median	x
Q1, Q3	xx.x, xx.x
Minimum, Maximum	xx.x, xx.x

F: Frequency endpoints will be presented by a 3-point summary using the following reporting structure, unless otherwise noted,

n	x
Count (%)	x (xx.x)

MF Categorical variables (multiple frequency) will be presented by a 3-point summary using the following reporting structure, unless otherwise noted, where the sum of the category n's is the total n

n	x
Category 1 count (%)	x (x.x)
Category 2 count (%)	x (x.x)

KM: Time to event summaries will be summarized with the following reporting structure:

Time to First Event	
Median (95% CI)	xx.x (xx.x, xx.x)
Q1, Q3	xx.x, xx.x
Minimum, Maximum	xx.x, xx.x
Total Number Censored	x
P-Value vs. Placebo	0.xxxx

IEAC-assessed clinical cure rate at TOC in the primary analysis population will be summarized as follows:

	Standard IV Therapy (N = xx)	Telavancin (N = xx)	Difference in Cure Rates Telavancin – Standard Therapy Difference (95% CI)
Cure	XX (XX.X%)	XX (XX.X%)	XX.X% (XX.X% , XX.X%)
Failure	XX (XX.X%)	XX (XX.X%)	
Indeterminate	XX (XX.X%)	XX (XX.X%)	
Missing	XX (XX.X%)	XX (XX.X%)	

Appendix 2: List of Nephrotoxic Medications

Source: \\theravance\thrx\DEPARTMENTS\BIOMETRICS_2700\SAS_PE\Dev\TD-6424\0112\csr\documents\ nephmeds_20180411_gg Note: Filter if Nephrotoxic=Y from Excel

Medication	Route of Administration	Nephrotoxic
ACECLOFENAC	ORAL	Y
ACEMETACIN	ORAL	Y
ACETAZOLAMIDE	ORAL	Y
ACETYLSALICYLIC ACID	ORAL	Y
ACICLOVIR	INTRAVENOUS	Y
ACICLOVIR	ORAL	Y
ADENOSINE	INTRAVENOUS	Y
AMIKACIN	INTRAVENOUS	Y
AMILORIDE W/HYDROCHLOROTHIAZIDE	ORAL	Y
AMOXI-CLAVULANICO	ORAL	Y
AMOXICILLIN	ORAL	Y
AMOXICILLIN W/CLAVULANATE POTASSIUM	INTRAVENOUS	Y
AMPHOTERICIN B	INTRAVENOUS	Y
AMPICILLIN	INTRAVENOUS	Y
ARTHROTEC	ORAL	Y
AZTREONAM	INTRAVENOUS	Y
BACTRIM	ORAL	Y
BENAZEPRIL	ORAL	Y
BENAZEPRIL HYDROCHLORIDE	ORAL	Y
BUMETANIDE	INTRAVENOUS	Y
BUMETANIDE	ORAL	Y
CANDESARTAN CILEXETIL	ORAL	Y
CAPTOPRIL	ORAL	Y
CARBOPLATIN	INTRAVENOUS	Y
CEFALEXIN	ORAL	Y
CEFAZOLIN	INTRAVENOUS	Y
CEFAZOLIN	WOUND IRRIGATION	Y
CEFOTETAN	INTRAVENOUS	Y
CEFRADINE	ORAL	Y
CEFTAZIDIME	INTRAVENOUS	Y
CEFTAZIDIME	INTRVITREAL	Y

Medication	Route of Administration	Nephrotoxic
CEFTIZOXIME	INTRAVENOUS	Y
CEFTRIAXONE	INTRAVENOUS	Y
CEFTRIAXONE	UNKNOWN	Y
CEFTRIAXONE SODIUM	INTRAVENOUS	Y
CEFUROXIME	INTRAVENOUS	y
CEFUROXIME	ORAL	Y
CELECOXIB	ORAL	Y
CHLOROTHIAZIDE	INTRAVENOUS	Y
CHLORTALIDONE	ORAL	Y
CILAZAPRIL	ORAL	Y
CLONIXIN	INTRAVENOUS	Y
CLOXACILLIN	INTRAVENOUS	Y
CO-DIOVAN	ORAL	Y
COLISTIN	NEBULIZED	Y
CONTRAST MEDIA	INTRAVENOUS	Y
CREATINE	ORAL	Y
DEXKETOPROFEN	INTRAVENOUS	Y
DEXKETOPROFEN TROMETAMOL	INTRAVENOUS	Y
DEXKETOPROFEN TROMETAMOL	ORAL	Y
DICLOFENAC	ORAL	Y
DICLOFENAC POTASSIUM	ORAL	Y
DICLOFENAC SODIUM	INTRAVENOUS	Y
DICLOFENAC SODIUM	ORAL	Y
DOXEPIN	ORAL	Y
DUOCID	INTRAVENOUS	Y
DYAZIDE	ORAL	Y
ENALAPRIL	ORAL	Y
ENALAPRIL MALEATE	INTRAVENOUS	Y
ENALAPRIL MALEATE	ORAL	Y
ENALAPRILAT	INTRAVENOUS	Y
ENOXAPARIN SODIUM	INTRAVENOUS	Y
ETODOLAC	ORAL	Y
ETORICOXIB	ORAL	Y
FLEET	RECTAL	Y
FLURBIPROFEN	INTRAVENOUS	Y

Medication	Route of Administration	Nephrotoxic
FOSINOPRIL	ORAL	Y
FOSINOPRIL SODIUM	ORAL	Y
FRUMIL	ORAL	Y
FUROSEMIDE	INTRAVENOUS	Y
FUROSEMIDE	ORAL	Y
GENTAMICIN	INTRAVENOUS	Y
HETASTARCH	INTRAVENOUS	Y
HYDROCHLOROTHIAZIDE	ORAL	Y
HYDROCHLOROTHIAZIDE W/LOSARTAN	ORAL	Y
HYZAAR	ORAL	Y
IBUPROFEN	ORAL	Y
INDAPAMIDE	ORAL	Y
INDOMETACIN	ORAL	Y
IODIXANOL	INTRAVENOUS	Y
IOHEXOL	INTRAVENOUS	Y
IOPROMIDE	INTRAVENOUS	Y
IRBESARTAN	ORAL	Y
KARVEA HCT	ORAL	Y
KETOPROFEN	INTRAVENOUS	Y
KETOROLAC	INTRAMUSCULAR	Y
KETOROLAC	INTRAVENOUS	Y
KETOROLAC TROMETHAMINE	INTRAMUSCULAR	Y
KETOROLAC TROMETHAMINE	INTRAVENOUS	Y
KETOROLAC TROMETHAMINE	ORAL	Y
LISINOPRIL	ORAL	Y
LISINOPRIL DIHYDRATE	ORAL	Y
LORNOXICAM	INTRAMUSCULAR	Y
LORNOXICAM	INTRAVENOUS	Y
LOSARTAN	ORAL	Y
LOSARTAN POTASSIUM	ORAL	Y
MANNITOL	INTRAVENOUS	Y
MELOXICAM	ORAL	Y
METAMIZOLE	INTRAVENOUS	Y
METAMIZOLE SODIUM	INTRAVENOUS	Y
METAMIZOLE SODIUM	ORAL	Y

Medication	Route of Administration	Nephrotoxic
METOCLOPRAMIDE	INTRAMUSCULAR	Y
METOLAZONE	ORAL	Y
MINOCYCLINE	ORAL	Y
NAFCILLIN	INTRAVENOUS	Y
NAPROXEN	ORAL	Y
NAPROXEN SODIUM	ORAL	Y
NESIRITIDE	INTRAVENOUS	Y
OLMESARTAN	ORAL	Y
OLMESARTAN MEDOXOMIL	ORAL	Y
OXACILLIN	INTRAVENOUS	Y
PARECOXIB	INTRAVENOUS	Y
PENICILLIN NOS	INTRAVENOUS	Y
PERINDOPRIL	ORAL	Y
PERINDOPRIL ERBUMINE	ORAL	Y
PIPERACILLIN	INTRAVENOUS	Y
PIPERACILLIN W/TAZOBACTAM	INTRAVENOUS	Y
PIROXICAM	ORAL	Y
PRITORPLUS	ORAL	Y
QUINAPRIL	ORAL	Y
QUINAPRIL HYDROCHLORIDE	ORAL	Y
RAMIPRIL	ORAL	Y
ROFECOXIB	ORAL	Y
SODIUM PHOSPHATE	INTRAVENOUS	Y
SODIUM PHOSPHATE	RECTAL	Y
SPEKTRAMOX	INTRAVENOUS	Y
SPIRONOLACTONE	ORAL	Y
SULINDAC	ORAL	Y
SULTAMICILLIN	INTRAVENOUS	Y
TACROLIMUS	ORAL	Y
TACROLIMUS	TOPICAL	Y
TELMISARTAN	ORAL	Y
TORASEMIDE	INTRAVENOUS	Y
TORASEMIDE	ORAL	Y
TRANDOLAPRIL	ORAL	Y
TRIAMTERENE	ORAL	Y

Medication	Route of Administration	Nephrotoxic
TRICHLORMETHIAZIDE	ORAL	Y
VALSARTAN	ORAL	Y
VANCOMYCIN	INTRAVENOUS	Y
VANCOMYCIN	INTRAVITREAL	Y
VANCOMYCIN	TOPICAL	Y
VANCOMYCIN	URETERAL	Y
VASERETIC	ORAL	Y
VERAPAMIL	ORAL	Y
VERAPAMIL HYDROCHLORIDE	ORAL	Y

Appendix 3: List of Antibiotic Medications

Source:\\theravance\thrx\DEPARTMENTS\BIOMETRICS_2700\SAS_PE\Dev\TD-6424\0112\documents\Antibiotics_20180411_gg

Medication	Route of Administration	MRSA Coverage	MSSA Coverage	Systemic
AMIKACIN	INTRAVENOUS	yes	yes	yes
AMOXI-CLAVULANICO	ORAL	No	Yes	yes
AMOXICILLIN	ORAL	No	Yes	yes
AMOXICILLIN W/CLAVULANATE POTASSIUM	INTRAVENOUS	no	yes	yes
AMPICILLIN	INTRAVENOUS	no	yes	yes
AUGMENTIN	INTRAVENOUS	no	yes	yes
AUGMENTIN	ORAL	no	yes	yes
AZITHROMYCIN	INTRAVENOUS	no	yes	yes
AZITHROMYCIN	ORAL	no	yes	yes
AZTREONAM	INTRAVENOUS	no	no	yes
BACTRIM	ORAL	yes	yes	yes
CEFALEXIN	ORAL	no	yes	yes
CEFAZOLIN	INTRAVENOUS	no	yes	yes
CEFAZOLIN	WOUND IRRIGATION	no	no	no
CEFDINIR	ORAL	no	yes	yes
CEFEPIME	INTRAVENOUS	no	yes	yes
CEFEPIME HYDROCHLORIDE	INTRAVENOUS	no	yes	yes
CEFTAROLINE	INTRAVENOUS	yes	yes	yes
CEFTAZIDIME	INTRAVENOUS	no	yes	yes
CEFTAZIDIME	INTRVITREAL	no	no	no
CEFTRIAXONE	INTRAVENOUS	no	yes	yes
CEFTRIAXONE	UNKNOWN	no	yes	yes
CEFTRIAXONE SODIUM	INTRAVENOUS	no	yes	yes
CEFUROXIME	INTRAVENOUS	no	yes	yes
CEFUROXIME	ORAL	no	yes	yes
CIPROFLOXACIN	INTAOCCULAR	no	no	no
CIPROFLOXACIN	INTRACCCULAR	no	no	no
CIPROFLOXACIN	INTRAVENOUS	no	possible	yes
CIPROFLOXACIN	ORAL	no	possible	yes

Medication	Route of Administration	MRSA Coverage	MSSA Coverage	Systemic
CIPROFLOXACIN HYDROCHLORIDE	INTRAVENOUS	no	possible	yes
CLINDAMYCIN	INTRAVENOUS	possible	yes	yes
CLINDAMYCIN	ORAL	no	yes	yes
CLINDAMYCIN HYDROCHLORIDE	ORAL	yes	yes	yes
CLINDAMYCIN PHOSPHATE	INTRAVENOUS	no	yes	yes
CLOXACILLIN	INTRAVENOUS	no	yes	yes
DAPTOMYCIN	INTRAVENOUS	yes	yes	yes
DOXYCYCLINE	ORAL	possible	possible	yes
DOXYCYCLINE HYCLATE	ORAL	possible	possible	yes
DOXYCYCLINE MONOHYDRATE	ORAL	possible	possible	yes
DUOCID	INTRAVENOUS	no	yes	yes
ERTAPENEM	INTRAVENOUS	no	yes	yes
FLUCLOXACILLIN	OPHTHALMIC	no	no	no
FLUCONAZOLE	INTRAVENOUS	no	no	yes
FLUCONAZOLE	ORAL	no	no	yes
FOSFOMYCIN	INTRAVENOUS	yes	yes	yes
FOSFOMYCIN TROMETAMOL	ORAL	yes	yes	yes
GENTAMICIN	INTRAVENOUS	yes	yes	yes
GENTAMICIN	OPHTHALMIC	yes	yes	no
KETOCONAZOLE	ORAL	no	no	yes
LEVOFLOXACIN	INTRAVENOUS	no	yes	yes
LEVOFLOXACIN	ORAL	no	yes	yes
LINEZOLID	INTRAVENOUS	yes	yes	yes
LINEZOLID	ORAL	yes	yes	yes
MEROPENEM	INTRAVENOUS	no	yes	yes
MEROPENEM TRIHYDRATE	INTRAVENOUS	no	yes	yes
METHENAMINE HIPPURATE	ORAL	no	no	no
METRONIDAZOLE	INTRAVENOUS	no	no	yes
METRONIDAZOLE	ORAL	no	no	yes
MICONAZOLE NITRATE	TOPICAL	no	no	no
MINOCYCLINE	ORAL	possible	yes	yes
MOXIFLOXACIN	INTRAVENOUS	yes	yes	yes
NAFCILLIN	INTRAVENOUS	no	yes	yes

Medication	Route of Administration	MRSA Coverage	MSSA Coverage	Systemic
NITROFURANTOIN	ORAL	no	no	yes
OFLOXACIN	OPHTHALMIC	no	no	no
OXACILLIN	INTRAVENOUS	no	yes	yes
PENICILLIN NOS	INTRAVENOUS	no	possible	yes
PIPERACILLIN	INTRAVENOUS	no	yes	yes
PIPERACILLIN W/TAZOBACTAM	INTRAVENOUS	no	yes	yes
PRIMAXIN	INTRAVENOUS	no	yes	yes
RIFAMPICIN	INTRAVENOUS	yes	yes	yes
RIFAMPICIN	ORAL	yes	yes	yes
SPEKTRAMOX	INTRAVENOUS	no	yes	yes
SULTAMICILLIN	INTRAVENOUS	no	yes	yes
TAZOBACTAM	INTRAVENOUS	no	no	yes
TEICOPLANIN	INTRAVENOUS	yes	yes	yes
TELAVANCIN	INTRAVENOUS	yes	yes	yes
TOBRAMYCIN	INTRAVENOUS	yes	yes	yes
UNACID	INTRAVENOUS	no	yes	yes
VANCOMYCIN	INTRAVENOUS	yes	yes	yes
VANCOMYCIN	INTRAVITREAL	yes	yes	no
VANCOMYCIN	ORAL	no	no	no
VANCOMYCIN	TOPICAL	no	no	no

Appendix 4: List of Coded Pathogens

Source: \\theravance\thrx\DEPARTMENTS\BIOMETRICS_2700\SAS_PE\Dev\TD-6424\0112\csr\documents\pathogens_20180326

Pathogen	Pathogen Updated
ACINETOBACTER BAUMANII	
ACINETOBACTER BAUMANNII	
ACITENOBACTER BAUMANNII	
ACTINOBACTER BAUMANNII	
AEROCOCCUS VIRIDANS	
ASPERGILLUS NIGER	
CANDIDA ALBICANS	
CANDIDA GLABRATA (TORULOPSIS GLABRATE)	
CITROBACTER FREUNDI	
CITROBACTER KOSERI	
CLOSTRIDIUM DIFFICILE	
COAG NEGATIVE STAPH (S. EPIDERMIDIS)	
ENTEROBACTER CLOACAE SPECIES COMPLEX	
ENTEROBACTER CLOACIAE	
ENTEROBACTER CLOCAE	
ENTEROBACTER SPECIES	
ENTEROCOCCUS FAECALIS	
ENTEROCOCCUS FAECIUM	
ESCHERICHIA COLI	
GROUP A STREP (S. AGALACTIAE)	
GROUP B STREP (S. PYOGENES)	
GROWTH	
KLEBSIELLA PNEUMONIA	
MRSA	
MSSA	
PROBABLE PROPIONIBACTERIUM SPECIES	
PROTEUS MIRABILIS	
PSEUDOMONAS AERUGINOSA	
ROTHIA SP. (ROTHIA TERRAE)	
S. AUREUS SUSCEPTIBILITY UNKNOWN	
SERRATIA MARCESCENS	
SPHINGOMONAS PAUCIMOBILIS	
STAPH LUGDUNESIS	
STAPH SAPROPHYTICUS	
STAPHYLOCOCCUS AUREUS	

Pathogen	Pathogen Updated
STAPHYLOCOCCUS EPIDERMIDIS	
STAPHYLOCOCCUS HAEMOLYTICUS	
STAPHYLOCOCCUS HOMINIS	
STAPHYLOCOCCUS HOMINIS SS. HOMINIS	
STAPHYLOCOCCUS HOMINIS SSP HOMINIS	
STAPHYLOCOCCUS WARNERI	
STREPTOCOCCUS AGALACTIAE	
STREPTOCOCCUS ANGINOSUS	
STREPTOCOCCUS GALLOLYTICUS	
VIRIDANS GROUP STREPTOCOCCUS	
YEAST	

Appendix 5: Coding Categories for Reason of Failure

REASON	ORIGINAL PROTOCOL	Map to
New Foci of Metastatic S Aureus Infect	Amendment 3	New Foci of Metastatic S Aureus Infection after Day 8
Subj Did Not Meet All Criteria	Amendment 1	Did Not Meet All Criteria for Clinical Success
Subj Did Not Meet All Criteria	Amendment 2	Did Not Meet All Criteria for Clinical Success
Subj Did Not Meet All Criteria	Amendment 3	Did Not Meet All Criteria for Clinical Success
Subj Discon SD Against Medical Advice	Amendment 3	Discontinued Study Drug against Medical Advice
Subj Discontinued SD due to AE	Amendment 1	Discontinued Study Drug due to Adverse Event and Required Further Antibacterial Therapy for S Aureus Infection before or at This Visit
Subj Discontinued SD due to AE	Amendment 2	Discontinued Study Drug due to Adverse Event and did Not Complete the Minimum Assigned Duration of Treatment
Subj Discontinued SD due to AE	Amendment 3	Discontinued Study Drug due to Treatment-emergent, Drug-related Adverse Event
Subj Rcvd Pot Effective Non-study Anti	Amendment 2	Received Potentially Effective Non-study Antibiotic before or at This Visit
Subj Rcvd Pot Effective Non-study Anti	Amendment 3	Received Potentially Effective Non-study Antibiotic before or at This Visit
Subj Req Further Study Anti Therapy	Amendment 2	Required Further Study Antibacterial Therapy for the S. aureus Infection Beyond Assigned Treatment Duration
Subj Req Further Study Anti Therapy	Amendment 3	Required Further Study Antibacterial Therapy for the S. aureus Infection beyond Assigned Treatment Duration, except Oral Prophylaxis
Subj Switch Antibiotic Lack of CR or AE	Amendment 2	Switched Study Antibiotic due to Lack of Clinical Response or Adverse Event
Subj Switch Antibiotic Lack of CR or AE	Amendment 3	Switched Study Antibiotic due to Lack of Clinical Response or an Adverse Event
Subject Remains Lost to Follow-up	Amendment 3	Remains Lost to Follow-up
Subject Withdrew Consent	Amendment 2	Withdrew Consent

Appendix 6: Summary of TFLs

Number	Title	Safety	mAT+
14.1.1.1	Enrollment By Investigator- All Randomized	NA	NA
14.1.1.3	Analysis Populations	NA	NA
14.1.1.4	Subject Disposition		X
14.1.2.1	Demographics And Baseline Characteristics		X
14.1.2.2	Classification Of Infection Type		X
14.1.2.3	Summary Of Baseline Clinical Characteristics		X
14.1.2.4	Summary Of Pathogens Isolated From Blood Cultures By The Site		X
14.1.2.5	Summary Of Pathogens Isolated From Blood Cultures By Central Lab		X
14.1.2.6	Summary Of Pathogens Isolated From Blood Cultures By The Site Or Central Lab		X
14.1.2.7	Summary Of Signs And Symptoms Of Bacteremia At Enrollment		X
14.1.2.8	Summary Of The Characteristics Of Bacteremia At Enrollment		X
14.1.2.9	Summary Of Risk Factors For Bacteremia		X
14.1.2.10	Summary of the Baseline modified APACHE II Scores And Components		X
14.1.3.1	Summary Of Select Medical History		X
14.1.3.2	Medical History	X	
14.2.1.1	Summary Of Adjudicated Clinical Outcome At Test-Of-Cure		X
14.2.1.2	Summary Of Adjudicated Clinical Outcome At Test-Of-Cure By Analysis Population		X
14.2.1.3	Summary Of Adjudicated Clinical Outcome At Test-Of-Cure By Subgroups (Mat UCB, CB, and RIE)		X
14.2.1.4	Summary Of Adjudicated Clinical Outcome At Test-Of-Cure By Subgroups (ME UCB, CB, and RIE)		X
14.2.1.5	Reasons For Failure Or Indeterminate In Clinical Response At Test-Of-Cure (Investigator-Assessed)		X

Number	Title	Safety	mAT+
14.2.2.1	Summary Of Adjudicated Clinical Response At End Of Treatment		X
14.2.2.2	Summary Of Adjudicated Clinical Response At End Of Treatment By Analysis Population		X
14.2.2.3	Summary Of Adjudicated Clinical Response At End Of Treatment By Subgroups (Mat UCB, CB, and RIE)		X
14.2.2.4	Summary Of Adjudicated Clinical Response At End Of Treatment By Subgroups (Me UCB, CB, and RIE)		X
14.2.2.5	Reasons For Failure Or Indeterminate In Clinical Response At End Of Treatment (Investigator-Assessed)		X
14.2.3.1	Summary Of Investigator Clinical Outcome At Test-Of-Cure		X
14.2.3.2	Summary Of Investigator Clinical Outcome At Test-Of-Cure By Analysis Population		X
14.2.3.3	Summary Of Investigator Clinical Outcome At Test-Of-Cure By Subgroups (Mat UCB, CB, and RIE)		X
14.2.3.4	Summary Of Investigator Clinical Outcome At Test-Of-Cure By Subgroups (ME UCB, CB, and RIE)		X
14.2.4.1	Summary Of Investigator Clinical Response At End Of Treatment		X
14.2.4.2	Summary Of Investigator Clinical Response At End Of Treatment By Analysis Population		X
14.2.4.3	Summary Of Investigator Clinical Response At End Of Treatment By Subgroups (Mat UCB, CB, and RIE)		X
14.2.4.4	Summary Of Investigator Clinical Response At End Of Treatment By Subgroups (Me UCB, CB, and RIE)		X
14.2.5.1	Summary Of The Time To Initial Clearance Of S. Aureus Bacteremia		X
14.2.6.1	Summary Of The 28-Day Mortality		X
14.2.6.2.1	Summary Of The 28-Day Mortality by Baseline CrCL <50		X
14.2.6.2.2	Summary Of The 28-Day Mortality by Baseline CrCL >=50		X
14.3.1.1	Study Drug Exposure And Compliance	X	
14.3.1.2	Study Drug Exposure And Compliance by Infection Type	X	
14.3.3.1	Overall Summary Of Adverse Events	X	
14.3.3.2	Treatment-Emergent Adverse Events By System Organ Class And Preferred Term	X	

Number	Title	Safety	mAT+
14.3.3.3	Treatment-Emergent Adverse Events By Preferred Term	X	
14.3.3.4	Treatment-Emergent Adverse Events By System Organ Class And Preferred Term Occurring In More Than 5% Of Study Population	X	
14.3.3.5	Treatment-Emergent Adverse Events By System Organ Class, Preferred Term And Severity	X	
14.3.3.6	Moderate Or Severe Treatment-Emergent Adverse Events By System Organ Class And Preferred Term	X	
14.3.3.7	Serious Adverse Events	X	
14.3.3.8	Deaths During Or Post Study	X	
14.3.3.9	Drug-Related Treatment-Emergent Adverse Events By System Organ Class And Preferred Term	X	
14.3.3.10	Drug-Related Treatment-Emergent Adverse Events By System Organ Class And Preferred Term And Severity	X	
14.3.3.11	Moderate Or Severe Drug-Related Treatment-Emergent Adverse Events By System Organ Class And Preferred Term	X	
14.3.3.12	Drug-Related Serious Adverse Events	X	
14.3.3.13	Adverse Events Leading To Premature Study Drug Discontinuation	X	
14.3.3.14	Adverse Events Leading To Temporary Interruption Of Study Drug	X	
14.3.3.15	Renal Adverse Events	X	
14.3.4.1.1	Hematology	X	
14.3.4.2.1	Serum Chemistry	X	
14.3.4.3.1	Urinalysis	X	
14.3.4.1.2	Hematology: Shift From Baseline	X	
14.3.4.2.2	Serum Chemistry: Shift From Baseline	X	
14.3.4.3.2	Urinalysis: Shift From Baseline	X	
14.3.4.4.1	Summary Of Change From Baseline Of Central Lab Creatinine And Creatinine Clearance By Time Points	X	

Number	Title	Safety	mAT+
14.3.4.4.2	Summary Of Last And Worst Creatinine Clearance Change From Baseline	X	
14.3.5.1	Vital Signs – Heart Rate	X	
14.3.5.2	Vital Signs – Respiration Rate	X	
14.3.5.3	Vital Signs – Systolic Blood Pressure	X	
14.3.5.4	Vital Signs – Diastolic Blood Pressure	X	
14.3.6.1	Prior Systemic Antimicrobials	X	
14.3.6.2	Concomitant Systemic Antimicrobials	X	
14.3.6.3	Post Study Drug Systemic Antimicrobials	X	
14.3.6.4	Nephrotoxic Medications Prior to Study Drug	X	
14.3.6.5	Concomitant Nephrotoxic Medications	X	
14.3.6.6	Post Study Drug Nephrotoxic Medications	X	
14.3.6.7	Prior Medications	X	
14.3.6.8	Concomitant Medications	X	
14.3.6.9	Post Study Drug Medications	X	
14.3.7.1.1	Electrocardiogram Summary: HR	X	
14.3.7.1.2	Electrocardiogram Summary: PR	X	
14.3.7.1.3	Electrocardiogram Summary: QRS	X	
14.3.7.1.4	Electrocardiogram Summary: QT	X	
14.3.7.1.5	Electrocardiogram Summary: QTcB	X	
14.3.7.1.6	Electrocardiogram Summary: QTcF	X	
14.3.7.1.7	Electrocardiogram Summary: RR	X	

Number	Title	Safety	mAT+
14.3.7.2	Electrocardiogram Threshold Summary	X	
14.3.7.3	Electrocardiogram Outlier Summary by Visit and Time Point	X	
14.3.8.1.1	Echocardiogram: Left Atrial and Ventricular Volumes and LVEF	X	
14.3.8.1.2	Echocardiogram: LVOT and HR	X	
14.3.8.1.3	Echocardiogram: Regurgitation and Vegetation	X	
14.3.8.1.4	Echocardiogram: Quality Evaluation	X	
14.3.8.1.5	Echocardiogram Endocarditis Assessment Through Day 8	X	

Listings

Number	Title	Population
16.2.1.1	Disposition and Analysis Sets	All Randomized Subjects
16.2.2.1	Protocol Versions	All Randomized Subjects
16.2.2.2	Major Protocol Deviations	All Randomized Subjects
16.2.4.1.1	Clinical Outcomes	AT
16.2.7.1	Adverse Events	All Randomized Subjects
16.2.7.2.1	Renal Adverse Events	Safety
16.2.7.2.2	Renal Replacement During Study	Safety
16.2.4.2.4.1	Demographics	AT
16.2.4.2.4.2	Relevant Medical History	AT
16.2.4.2.4.3	General and Relevant Medical History	AT
16.2.4.2.4.4	Baseline modified APACHE II Scores and Components	AT
16.2.5.3.2	Prior and Concomitant Medications	Safety
16.2.5.3.3	Prior and Concomitant Nephrotoxic Medications	Safety
16.2.5.3.4	Antimicrobial Therapy	All Randomized Subjects
16.2.6.2.1	Microbiology: Blood Cultures	AT
16.2.6.2.2	Microbiology: Specimens Other Than Blood Cultures	Safety
16.2.8.1.1.1	Central Laboratory Tests: Hematology: Part 1	Safety
16.2.8.1.1.2	Central Laboratory Tests: Hematology: Part 2	Safety
16.2.8.1.1.3	Central Laboratory Tests: Hematology: Part 3	Safety
16.2.8.1.1.4	Central Laboratory Tests: Hematology: Part 4	Safety
16.2.8.1.1.5	Central Laboratory Tests: Hematology: Part 5	Safety
16.2.8.1.1.6	Local Laboratory Tests: Hematology: White Blood Cells	Safety
16.2.8.1.1.7	Central Lab Hematology: Abnormal Differentials	Safety

Number	Title	Population
16.2.8.1.2.1	Central Laboratory Tests: Serum Chemistry: Part 1	Safety
16.2.8.1.2.2	Central Laboratory Tests: Serum Chemistry: Part 2	Safety
16.2.8.1.2.3	Central Laboratory Tests: Serum Chemistry: Part 3	Safety
16.2.8.1.2.4	Central Laboratory Tests: Creatine Kinase, C-reactive Protein, and Interleukin 10	Safety
16.2.8.1.2.5	Central Laboratory Tests: Creatinine and Creatinine Clearance	Safety
16.2.8.1.2.6	Local Laboratory Tests: Creatinine and Creatinine Clearance	Safety
16.2.8.1.3.1	Central Laboratory Urinalysis: Qualitative	Safety
16.2.8.1.3.2	Central Laboratory Urinalysis: Quantitative	Safety
16.2.8.1.3.3	Central Laboratory Urinalysis: Other Findings	Safety
16.2.9.1.1	Vital Signs	Safety
16.2.9.1.2	Temperature Log	Safety
16.2.11.1	12-lead Safety Electrocardiogram	Safety
16.2.11.2	12-lead Safety Electrocardiogram QTcF >500 msec or QTcF Increase >60 msec	Safety
16.2.12.1	Echocardiogram: Left Atrial and Ventricular Volumes and LVEF	Safety
16.2.12.2	Echocardiogram: LVOT and HR	Safety
16.2.12.3	Echocardiogram: Regurgitation and Vegetation Part 1 of 2	Safety
16.2.12.4	Echocardiogram: Regurgitation and Vegetation Part 2 of 2	Safety
16.2.12.5	Echocardiogram: Quality Evaluation and Comment	Safety
16.2.12.6	Echocardiogram Endocarditis Assessment Through Day 8	Safety

Figures

Number	Title	Figure Type	ITT	PP	Safety
15.2.1.1.1	Kaplan-Meier Survival Function: Time to initial clearance of S. aureus bacteremia with censoring at Day 8		X	X	
15.2.1.1.2	Kaplan-Meier Survival Function: Time to initial clearance of S. aureus bacteremia with no censoring		X	X	
15.2.1.2	Kaplan-Meier Survival Function: Days from Last Treatment Day to Test of Cure Visit		X	X	
15.2.1.3	Kaplan-Meier Survival Function: 28-day all-cause mortality		X	X	X
15.2.1.3.1	Kaplan-Meier Survival Function: 28-day all-cause mortality by baseline CrCL <50		X	X	X
15.2.1.3.2	Kaplan-Meier Survival Function: 28-day all-cause mortality by baseline CrCL >=50		X	X	X