1. TITLE PAGE

Statistical Analysis Plan

DMID Protocol Number: 09-0080 Version 4

A Multi-Center, Randomized, Open-Label, Comparative Study to Assess the Safety and Efficacy of a Treatment Algorithm to Reduce the Use of Vancomycin in Adult Patients with Blood Stream Infections due to Staphylococci

Date of Analysis Plan
December 12, 2013

2. LIST OF TABLES/FIGURE/LISTINGS

3. LIST OF ABBREVIATIONS

Abbreviation	Term
ABT	Algorithm-Based Treatment
AE	Adverse Event
Algorithm	Algorithm Based Therapy
Alpha	Statistical Significance Level
ANOVA	Analysis of Variance
CEC	Clinical Event Committee
CMH test	Cochran-Mantel-Haenszel Test
CoNS	Coagulase Negative Staphylococcus
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
ITT	Intent-to-treat
IVRS	Interactive Voice Randomization System
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentrations
PENSPP	Potentially Effective Non-study AntibioticPer protocol Population
PPE	Per Protocol Population after excluding the patients with complicated staphylococcal infection
SAE	Serious Adverse Event/Serious Adverse Experience
SOC	Standard of Care
TOC	Test of Cure

4. INTRODUCTION

The algorithm-based treatment study with staphylococcal blood stream infection evaluates the safety and efficacy of a treatment algorithm to reduce the use of vancomycin in adult patients with blood stream infections due to staphylococci. This statistical analysis plan was developed based on the information contained in the study protocol DMID 09-0080. Tables, Figures and Listings of DSMB and final study reports are displayed in separate documents. The purpose of this analysis plan is to provide a detailed description of the planned statistical analysis of the safety and efficacy endpoints presented for monthly safety monitoring, DSMB, and final study reports.

4.1 Study Design

This is a phase 2, multi-center, randomized, open-label comparative study to assess the safety and efficacy of a treatment algorithm to reduce the use of vancomycin in adult patients with blood stream infections due to staphylococci. It is a multicenter trial conducted in 16 sites- 15 sites in the United States (US) and 1 site in Spain. The study will last about six years. The total enrollment is of approximately 500 patients at least 18 years of age who have a blood stream infection with staphylococci (see details in Sample size and Power section). Randomization will be 1:1 Algorithm vs SOC in permuted randomized blocks by site using an interactive voice randomization system (IVRS). As the primary safety and efficacy endpoint, cure rate will be recorded at Final Test of Cure (TOC) evaluation following last dose of antibiotic, which will be evaluated at 28 $\pm$ 4 days for CoNS infections and at 42 $\pm$ 4 days for S. aureus infections by telephone call or clinic visit. Early TOC, by telephone call or clinic visit, will be recorded between [10, 24] days for CoNS and [17, 31] days for S.aureus infections. If patient terminates study early for any reason, TOC assessment should be performed at the time of termination.

Safety analysis will include analysis of all AEs leading to study drug withdrawal and all SAEs recorded on case report form, and the incidence rates of change from vancomycin or a protocol-approved study antibiotic to another protocol-approved study antibiotic due to AE associated with study drug. In order to demonstrate that algorithm-based treatment of patients with blood stream infection can decrease antimicrobial usage when compared to current SOC, duration of treatments will be compared as our secondary efficacy endpoint.

Table 1 Mode of treatment administration—Days of Vancomycin Use

Days of treatment--Vancomycin*	Identified Organism				
	S. aureus[1]		CoNS[2]		
	uncomplicated	complicated	simple	uncomplicated	complicated
Algorithm	14(±2)	28-42(±2)	1-3(+1) [3] ; 0-Randomization(+1) [4]	5(±1)	7-28(±2)
SOC	14-28(±2)	28-42(±2)	4(±1)	10(±1)	7-28(±2)

*: See Table 2 for Vancomycin alternatives by clinical setting.

S. aureus[1]: Final TOC(early TOC) at 42 ± 4(17-31) days following last dose of antibiotic.

CoNS[2] : Final TOC(early TOC) at 28 ± 4 (10-24) days following last dose of antibiotic.

[3] : Based on protocol prior v4; [4] : Based on protocol v4.

Table 2: Vancomycin Alternatives by Clinical Setting*

Antibiotic	Dosing	Comments
Vancomycin alternative antibiotics for methicillin susceptible staphylococci		
US - Nafcillin, Oxacillin Spain – Cloxacillin	2 gm q 4h IV, or equivalent dosing through continuous infusion, in algorithm arm(dosing per SOC in SOC arm)	Preferred agents for MSSA and susceptible CoNS. If penicillin-allergic or intolerant, may use vancomycin instead
Penicillin	4 million units q4h IV or equivalent dosing through continuous infusion, in algorithm arm (dosing per SOC in SOC arm)	
Cefazolin	1.5 gm q 6h IV or equivalent, e.g. 2 gm q 8h IV**, renally dose-adjusted per	In the US, may use for *S. aureus* only, per FDA indication. In Spain, may use for any methicillin-susceptible

	package insert	staphylococci
Vancomycin alternative antibiotics for methicillin resistant staphylococci		
US - Daptomycin*** Spain – Cubicin	6 mg/kg IV q 24h in algorithm arm(dosing per SOC in SOC arm)	Use only if unable to give vancomycin due to allergy, intolerance, elevated vancomycin MIC, or AE/SAE

*any antibiotic may be utilized in SOC patients in order to follow standard clinical practice
**recommended dose per package insert is 1-1.5 g q 6h IV, which is equivalent to the 2 gm q 8h IV recommended by current guidelines, and less than the 12 g/day maximum dose allowed per package insert
***FDA-Approved for *S. aureus* bacteremia and right-sided endocarditis, including infections caused by methicillin resistant *S. aureus*.

In addition to the investigator evaluation of clinical outcomes, a Clinical Event Committee (CEC) will adjudicate the following events for at least 50 patients or ~ 12 patients per year for the 4 years of study enrollment: 1) establishing the presence and significance of PENS antibiotics; 2) evaluating patient outcome in a randomly selected cohort of study patients; and 3) adjudicate death for attribution. We will use the adjudicated outcomes if they are available.

4.2 Sample Size and Power

Sample size calculation (N=500) will be performed based on primary efficacy endpoint, which is the cure rate at final TOC. We assume that both treatments have an equal cure rate of 75%. Under a non-inferiority margin of 15% and a consideration of 28% drop out rate, with approximately 250 subjects per treatment, the study will have at least 90% power for establishing non-inferiority at a significance level of 5% (2-sided). See reference [1] chapter 4 for details about sample size calculation for testing non-inferiority.In order to validate these assumptions, and to confirm the appropriate target number of patients, a blinded sample size re-estimation will be performed after 250 patients have been enrolled and completed the final TOC visit, and also after 350 patients have been enrolled and completed the final TOC visit. The sample size re-estimation will be reviewed by the DSMB and the DSMB will provide recommendations. The Executive Committee will determine an appropriate course of action. If the sample size re-estimation performed at 350 patients enrolled confirms that at least 80% power can be achieved by enrolling 400 patients as indicated in Table 3 in the protocol, the total patient target will be reduced to 400 enrolled patients.

Patients who discontinue after beginning treatment will not be replaced; Patients who discontinue after randomization and before starting treatment will be replaced.

4.3 Randomization

Approximately 500 subjects will be randomized to one of two treatment arms (Algorithm and SOC) using an interactive voice randomization system (IVRS). Randomization will be 1:1 Algorithm vs SOC in permuted randomized blocks by site. The randomization code will be generated by statistician(s) at DCRI.

5. OBJECTIVES

5.1 Primary

The primary object of this trial is to (1) demonstrate that the clinical efficacy of algorithm-based treatment of patients with staphylococcal blood stream infection is noninferior to current standard of care (SOC); (2) evaluate the safety of algorithm-based treatment as an alternative to current SOC.

5.2 Secondary

The secondary object of this trial is to demonstrate that algorithm-based treatment of patients with staphylococcal blood stream infection can decrease antimicrobial usage when compared to current SOC.

6. SAFETY AND EFFICACY ENDPOINTS

6.1 Primary Endpoints

The primary efficacy endpoint is the cure rate of subjects who were classified as either "Success" (see Protocol sections 3.2.3.1 and 3.2.3.8), "Failure" (see Protocol section 3.2.3.1), or "Non-Evaluable" (see Protocol section 3.2.3.1) at final TOC.

Table 3: Definitions of Primary Endpoint Outcomes

Non-Evaluable [Protocol 3.2.3.1]	**Failure** [Protocol 3.2.3.1]
Meet the following Criteria: Failure for Administrative Reasons (e.g., patient withdraws consent for study participation; patient discontinues medical treatment against medical advice; patient withdrawn from the study; patient lost to follow-up) in patients who do not fail for other reasons.	Patients will be classified as "Failure" at or before final TOC if they meet any of the following Criteria*: a. Were judged "Failure" at early or final TOC by the Site PI or designated SI b. Treatment was changed due to Unsatisfactory Clinical Response defined as failure to resolve clinical manifestations of infection (e.g. fever, elevated WBC count). c. Had persisting or relapsing infection (Section 3.2.3.2 and Section 3.2.3.3, respectively). d. Identification of a New Complicated Staphylococcal Infection (Section 3.2.3.5) not known to be present at either randomization or after completion of study treatment for their baseline clinical classification of bacteremia. These patients will be retained in their original group and counted as treatment failures. e. Died prior to early or final TOC evaluation. * if patients fail prior to the final TOC visit, final TOC assessments can be conducted at the time of failure and the patient can be classified as completing the study at that time.

Success: Meet all of the following criteria defined by site PI or SI at final TOC, and exhibited none of the criteria of "Failure" or "Non- Evaluable" outcomes [Protocol 3.2.3.1/ 3.2.3.8]

	Simple CoNS[2]	Uncomplicated CoNS[2]	Complicated CoNS[2]	Uncomplicated *S. aureus*[1]	Complicated *S. aureus*[1]
negative follow-up blood culture	√	√	√	√	√
Clinical resolution of signs and symptoms	√	√	√	√	√

Exhibit none of the criteria for "Failure" or "Non-Evaluable" outcomes	√	√	√	√	√ and no additional sites of Complicated Staphylococcal Infection, up to the respective TOC
Population restriction:			Population comes from Simple or/and uncomplicated CoNS		Population comes from Uncomplicated *S. aureus*

S. aureus[1]: Final TOC(early TOC) at 42 ± 4(17-31) days following last dose of antibiotic.
CoNS[2] : Final TOC(early TOC) at 28 ± 4 (10-24) days following last dose of antibiotic.

Safety analysis will also include analysis of all AEs leading to study drug withdrawal and all SAEs recorded on case report form, and the incidence rates of change from vancomycin or a protocol-approved study antibiotic to another protocol-approved study antibiotic due to AE associated with study drug.

6.2 Secondary Endpoint

The secondary endpoint (see Protocol 3.2.1) is antibiotic days in support of the secondary objective for the Per protocol population after excluding the patients with a complicated staphylococcal infection after randomization but prior to the completion of study treatment for their baseline clinical classification of bacteremia (i.e., on PPE population).

6.3 Endpoints for Sensitivity Analyses

For assessment of the primary efficacy endpoint, missing values at final TOC assessment will be counted as missing, or imputed by early TOC for the sensitivity analysis.

6.4 Endpoints for Exploratory Analyses

The exploratory outcome measures include:
(a) Cure rate, the days of antibiotic, and days to discontinuation (using survival analysis methods) for the following diagnostics subgroups in the ITT and PP populations, respectively:
1. Cohort of CoNS
2. Sub-cohort of simple CoNS
3. Sub-cohort of Uncomplicated CoNS
4. Cohort of S. aureus Bacteremia
5. Sub-Cohort within uncomplicated S. aureus Bacteremia;
(b) Vancomycin MIC values to investigate potential associations to clinical outcomes (e.g., cure rates, duration of bacteremia on treatment, and incidence of development of new complicated staphylococcal infection).

The above cohorts recorded in INFORM, that were evaluated by site PIs, will also be compared by the derived cohort (defined in protocol Table 1).

7. STUDY POPULATION

● Intent-To-Treat (ITT) Population: All patients who are randomized in the study.
●Per Protocol Population (PP): Patients from ITT population meeting any of the following criteria will be EXCLUDED from PP analysis:

a) Received a PENS antibiotic
b) Did not undergo removal of intravascular catheter suspected to be infected. Note that patients with simple CoNS bacteremia may retain the catheter; all other patients should have their catheter(s) removed
c) Had blood stream infection with a vancomycin-resistant staphylococcus; or a staphylococcus resistant to protocol-identified alternative drugs if these were used
d) Discontinued study medication prematurely for reasons other than clinical failure
e) Did not undergo final TOC assessment
f) Did not comply with all Patient Inclusion Criteria as listed in 5.1.
g) Violated any Patient Exclusion Criteria as listed in 5.2.
h) Died within 3 days of randomization
i) Were classified as non-evaluable

●Per Protocol Population after excluding the patients with complicated staphylococcal infection (PPE): Patients from PP population who did not have a complicated staphylococcal infection.

● MITT Population: Subjects in ITT population and who either completed the study, or discontinued the study. This population is used for DSMB only if ITT and MITT are different.

8. HALTING RULES

The Data and Safety Monitoring Board (DSMB) will define halting rules in their charter. The DSMB will consider stopping the trial if one or more of the following conditions occur:

1. In the patients with simple or uncomplicated bacteremia, there is evidence that the incidence of SAEs in the algorithm group is >= 20% higher than the standard of care group (SOC) and is not by chance alone (defined as P-value <0.05).

2. In patients with simple or uncomplicated infections, the incidence of persisting and/or relapsing infections is >= 20% higher in the algorithm group than the SOC group and is not by chance alone (defined as P-value <0.05). See protocol sections 3.2.3.2 and 3.2.3.3 for definitions of persisting and relapsing infection.

3. In all randomized patients, there is >= 20% difference in the death rate between the SOC and algorithm group and is not by chance alone (defined as P-value <0.05).

To assure adequate data is available, halting rule analysis will be performed prior to DSMB meetings after 125, 250 and 350 patients have enrolled and completed the Test of Cure visit. The DSMB will evaluate the halting rule results during regularly scheduled DSMB meetings and will decide if the trial may proceed or should be stopped during each meeting.

9. STATISTICAL METHODS

9.1 General Analysis Conventions/Rules

● Continuous variables: Descriptive statistics for continuous variables will be displayed as the number of observations, mean, standard deviation, median, minimum, and maximum within the subjects with non-missing values. Efficacy data will be tabulated to count 3 categories: total number of subjects, success responders, number of subjects who had non-missing assessments.

● Discrete variables: Categorical variables will be provided with the counts and percentages in each category, within the subjects with non-missing values.

● Level of statistical significance: Unless specified otherwise, any tests of hypotheses are two-sided and the nominal level of significance will be 5%; and p-values will be obtained based on two-sided tests. No intra-block correlation will be assumed in statistical analysis of the collected data.
● Computer software: SAS statistical analysis software version 9.2 (or newer version), (SAS Institute, Cary, NC), will be used for statistical analyses on a UNIX operating system at DCRI.

9.2 Baseline Comparability

Patient disposition in terms of the number and percent of patients enrolled by site will be tabulated. The number of patients randomized, number completing the study, and reasons for discontinuation, reasons for exclusion from the PP population will be summarized by treatment group within each cohort. Patient demographics and baseline characteristics such as age, weight, route of acquisition of infection (nosocomial, health-care associated and community-acquired), and comorbid condition(s) will be tabulated and compared across treatment groups within each cohort. All comparisons will be performed by use of the Cochran-Mantel-Haenszel (CMH) test for categorical variables and two-way analysis of variance (ANOVA) for continuous variables. If statistically significant differences in demographic or patient characteristics (potential confounding risk factors) of the enrolled patients between treatments are detected, they will be used as the covariates adjusted in a logistic regression model (SAS LOGISTIC procedure) model for the primary endpoint. The odds ratios for ABT versus SOC together with the two-side 95% confidence intervals and corresponding p-values will be summarized. Similarly, if statistically significant differences for the parameters among the sites are detected, analysis of covariance (ANCOVA) will be performed to compare the days of antibiotic use between treatments with the confounding factor of site and the above parameters that have significant differences among sites.

9.3 Handling of Missing Data

Missing efficacy data will be handled as follows: subjects who had infection and missing values in efficacy variable at final TOC will be considered as treatment failure for the primary analyses. If a subject was randomized without infection, the efficacy variable will be missing, and will not be included in efficacy analysis.

For assessment of the primary endpoint, missing values will be counted as missing, and imputed by early TOC for the sensitivity analysis.

9.4 Handling of Duplicate Lab and EKG Data

Handling of duplicate lab and ECG records from 2 samples drawn at the same date is shown as follows:
If one of the duplicate records can be identified as the unscheduled one from source document, only the scheduled record will be included in the analyses.
If duplicate records are collected all for the scheduled visit for some reason, worst case scenario will be applied in the analyses.
All records will be included in the listings.

9.5 Patient Disposition, Discontinuation and Baseline Data

9.5.1 Patient Disposition, Discontinuation

Number of subjects randomized, treated, completing the study and reasons for discontinuation will be summarized by treatment group.

9.5.2 Demographics and Baseline Characteristics

In order to assess the baseline comparability of the treatment groups, relevant data on the following demographic and baseline characteristics will be tabulated by treatment and overall for the ITT and per protocol population.

Demographics and Baseline Characteristics: Age (years), Race, Ethnicity, Weight, BMI, route of acquisition of infection (nosocomial, health-care associated and community-acquired) and comorbid condition(s).

9.6 Concomitant Medications

Empiric treatment for Gram-negative pathogens is allowable; these agents will not be counted when calculating antibiotic days unless: 1) susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic, and 2) the patient is not receiving other protocol approved antistaphylococcal treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam therapy for gram-negative infection).

A Medical Coder will code concomitant medications using a current version of the WHODRL dictionary. The number and percent of patients taking concomitant medications will be tabulated by treatment group.

9.7 Statistical Analyses

9.7.1 Primary Analyses

The primary efficacy analysis is to compare cure rate between algorithm-based treatment and SOC treatment.

Point estimates and the corresponding two-sided 95% confidence intervals for the difference of cure rate in each treatment will be calculated. The large sample z-test for comparing the two proportions will be performed to test the inferiority with the pre-specified non-inferiority margin. The CMH test and ANOVA or ANCOVA will also be performed to compare the difference of the intrinsic differences in the clinical experiences and practices at each site, characteristics of enrolled patients(including route of acquisition of infection), and variations in administering antibiotic dosing schemas as appropriate. If there is statistically significant difference for the above parameters among the sites detected, the logistic regression model with the confounding factor(s), which had significant difference among sites, will be used to comparing the cure rate between treatments. The odds ratios of cure rate of algorithm-based treatment versus SOC therapy together with the 95% confidence intervals, corresponding p-value will be summarized.

Because safety will also be assessed as a primary endpoint in this trial, safety will be evaluated by comparing all SAEs in the algorithm-based treatment and SOC treatment.

9.7.2 Secondary Efficacy Analysis

The secondary analysis is to compare the days of antibiotic use between the algorithm-based treatment and SOC treatment for the PPE population, which includes subjects having simple CoNS, or uncomplicated CoNS, or uncomplicated S. aureus. For DSMB, compliance with study antibiotic days per protocol will be evaluated and compared by treatment.

Patients in the simple or uncomplicated cohort who develop new complicated staphylococcal infection after the completion of study treatment for their baseline clinical classification of bacteremia will be remained in their original group and counted as failure. They will be included in the PP analyses as treatment failures and their antibiotic days for their original grouping (e.g., the clinical group to which they had been assigned *before* being defined as having complicated infection) will be included in the Secondary analysis.

Patients in the simple or uncomplicated cohort who develop complicated staphylococcal infection after randomization but prior to the completion of effective treatment for their baseline clinical classification of bacteremia should remain in the PP analysis. Cure will be determined at their TOC visits. These patients will be regrouped in the complicated bacteremia population of the algorithm.

Point estimates and the corresponding two-sided 95% confidence intervals for the difference in the days of antibiotic use between the algorithm-based treatment and SOC will be calculated. ANCOVA will be performed to compare the days of antibiotic use between treatments after adjusting the organism and type of infections, and any significant confounding factor(s).

Extent of exposure to study medication will be presented in terms of treatment duration and mean daily dose. A summary table will be provided for dose compliance.

9.7.3 Sensitivity Analyses

Sensitivity analysis with respect to missing data imputation will be performed. More specifically, for the first step, we will construct the primary estimates and corresponding two-sided 95% confidence intervals denoted as (L, U) of cure rate by imputing method specified in Section 11.3.6; for the second step, we will construct the secondary estimates and corresponding two-sided 95% confidence intervals of cure rate without imputing the missing values, that is, treating missing as missing. If the secondary estimates drop in the corresponding (L, U), or their confidence intervals do overlay with the primary ones, then we can conclude that our primary analysis is robust. Otherwise, our conclusion based on the primary analysis will have limitations.

9.7.4 Exploratory Analyses

The exploratory analyses include comparisons of the treatment effects for the endpoints cure rate and the days of antibiotic for the following diagnostics subgroups in the ITT and PP populations, respectively:

1. Cohort of CoNS
2. Sub-cohort of simple CoNS
3. Sub-cohort of Uncomplicated CoNS
4. Cohort of S. aureus Bacteremia
5. Sub-Cohort within uncomplicated S. aureus Bacteremia

Table 4 Summary of Endpoints

Comparison	Endpoint	Population/Analysis
ABT vs SOC*	Cure rate at TOC	ITT/ Primary [1] PPE/ Secondary [1] ITT/ Sensitivity[2]
	Event rate of SAE Event rate of AEs leading to study drug withdrawal	ITT/ Primary PPE/ Exploratory
	Antibiotic days	PPE/ Secondary
CoNS: ABT vs SOC	Cure rate at TOC	ITT/ Exploratory [1] PPE/ Exploratory [1]
S. aureus: ABT vs SOC	Same as above	Same as above
CoNS-simple: ABT vs SOC	Same as above	Same as above
CoNS-uncomplicated: ABT vs SOC	Same as above	Same as above
S. aureus – uncomplicated: ABT vs SOC	Same as above	Same as above
CoNS: ABT vs SOC	Antibiotic days	ITT, PPE/Exploratory
S. aureus: ABT vs SOC	Same as above	Same as above
CoNS-simple: ABT vs SOC	Same as above	Same as above
CoNS-uncomplicated: ABT vs SOC	Same as above	Same as above
S. aureus – uncomplicated: ABT vs SOC	Same as above	Same as above
ABT vs SOC	●associations between vancomycin MIC values and clinical outcomes ●incidence of changing study medication due to AE ●Days to discontinuation since the first dose	ITT/ Exploratory PPE/ Exploratory

1 Missing at final TOC will be considered as treatment failure
2 Missing at final TOC will be considered as missing, and imputed by early TOC
*: perform the similar analysis after adjusting for the confounding factor of site and demographics and baseline characteristics , if they are significant by treatments.

In addition, potential associations between vancomycin MIC values and clinical outcomes (e.g., cure rates, duration of bacteremia on treatment, and incidence of development of new complicated staphylococcal infection) will be assessed as part of exploratory efficacy analyses.

9.8 Safety Analyses

The safety analyses will be performed within the ITT population. All AEs leading to study drug withdrawal and all SAEs will be collected and tabulated. The incidence rates of change vancomycin or a protocol-approved study antibiotic to another protocol-approved study antibiotic due to AE associated with study drug will also be tabulated by each treatment group. Separate tabulations will list events according to seriousness, maximum severity, and worst possible association with study drug. Other safety parameters, such as laboratory data, will also be listed and summarized.

9.8.1 Adverse Events

The number of subjects who have or report at least one adverse event (AE) during the study will be tabulated for each treatment group. The number of AEs reported by subject will be summarized for each treatment group. Subject frequency counts and percentages by MedDRA current version 14.0 and update version lock will be presented by maximum severity for each treatment group.

9.8.2 Laboratory Data

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for baseline values, actual values, changes from baseline, and percentage changes from baseline will be presented as appropriate by last visit, worst values (either minimum or maximum) among post-baseline visits, and treatment group for the following 16 tests-- hemoglobin, hematocrit, WBC, Platelet, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Total bilirubin, BUN, Creatinine, Calcium, Glucose, Potassium, Sodium.

Echocardiography will be performed on all algorithm subjects with a baseline blood culture positive for *S. aureus* . The TEE is preferred over the TTE. The echocardiogram will be interpreted by both the site's echocardiographer and an experienced echocardiographer at the DCRI Echocardiography Core Laboratory. A comparison between the site and central echocardiogram readings will be performed. If there are discrepancies, then only the site interpretation will be reported on the eCRF and used for clinical decision-making at the study site. Patient outcome at final TOC for those patients randomly selected for CEC adjudication of outcome will also be assessed by the CEC using the interpretation of the

Echocardiography Core Laboratory to ensure that no bias is introduced by the fact that the onsite clinicians interpreting the echocardiogram know the clinical condition of the patient.

9.8.3 Vital Signs

Summary statistics (n, mean, standard deviation, median, minimum and maximum) for baseline values, actual values, changes from baseline, and percentage changes from baseline will be presented as appropriate by treatment group for vital signs data, including systolic blood pressure, diastolic blood pressure, heart rate, and temperature.

10. MONTHLY SAFETY REPORT

The DSMB charter requests the DCRI to monitor the following event rates on a monthly basis:

1. In the patients with simple or uncomplicated bacteremia, compare the incidence of serious adverse events (SAEs) between the algorithm and standard of care arm
2. In patients with simple or uncomplicated infections, compare the incidence of persisting and/or relapsing infections between the algorithm and standard of care arm
3. In all randomized patients, compare the death rate between the algorithm and standard of care arms

DCRI will also calculate the Fisher's exact test comparing incidence rates between the two treatment groups, and send an e-mail alerting the study medical monitor if the test is significant at the 0.01 level. Table and listings shells are shown in Table 5, and listing 1-1 and listing 1-2, respectively.

The medical monitor will inform the DSMB chair, who will determine whether an unplanned DSMB meeting(s) should be convened to study and review the event(s) in more detail.

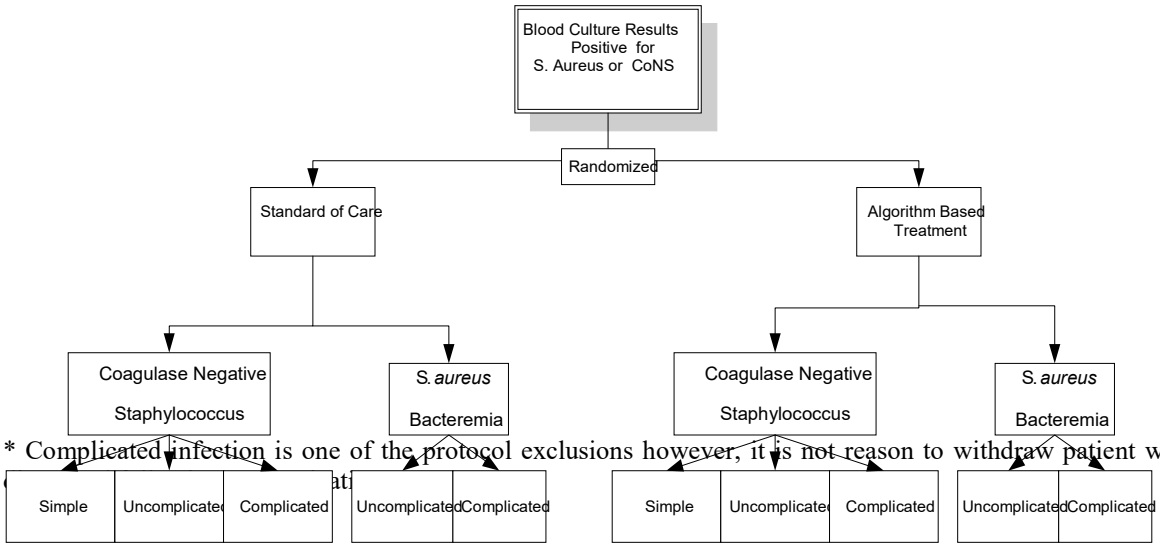
11. REFERENCES

[1]. Chow, S., Shao, J., and Wang, H. (2007). Sample Size Calculations in Clinical Research. Second Edition, Chapman and Hall/CRC Press, Taylor & Francis, New York, NY, Chapter 4. - For sample size calculation for testing non-inferiority.

12. REVISION HISTORY

Date	Version / Summary of Change
September 13, 2012	2nd draft, based on Protocol version 3.0 on August 26, 2011
April 20, 2011	1st draft
July 5, 2011	Adding imputation for TOC using early TOC for sensitivity analysis (section 9.3 2nd paragraph, Table 4)
August 4, 2011	Add the frequency of changing study drug into safety analysis, CEC description under section study design, add reasons for exclusion from PP population under baseline comparability section; add Days to discontinuation since the first dose in the exploratory analysis
Nov 19, 2012	Changed based on protocol amendment version 3.1_12
March 1, 2013	Changed based on protocol amendment version 3.1_26
December 12, 2013	Changed based on protocol amendment version 4.0_11 July 13 2013

Figure 1: Schematic of Study Design



* Complicated infection is one of the protocol exclusions however, it is not reason to withdraw patient when

Table 5: Summary of Halting Rules

ITT population	ABT N=	SOC N=	P value@
Number of subjects with simple or Uncomplicated bacteremia	N1/N (%)	N2/N (%)	---
SAEs*	N3/N1 (%) N4	N5/N2(%) N6	
Persisting and/or relapsing infections	N7/N1 (%) N8	N9/N2(%) N10	
Death—ITT population	N11/N (%)	N12/N(%)	

@: using Fisher's exact test

* Entry format: Number of subjects/Number of Eligible subjects (%) # of events

Generated based on data downloaded on DDMMMYYYY

Listing 1-1: List of subjects having SAEs, Persisting and/or relapsing infections and simple or uncomplicated bacteremia
--Number of Subjects

Treatment	Cohort	Having SAE	Having Persisting and/or relapsing infections

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Listing 1-2: List of dead subjects—ITT population (unique)

Treatment	Cohort	Subject#	Age/gender/race	Days since dose Day 1#	Events leading up to death

#:flag for the death related to study treatment

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