STATISTICAL ANALYSIS PLAN

Study Title

A Multicenter, Double blinded, Randomized, Parallel design, Phase IIa Clinical trial to evaluate the Efficacy, Safety and Pharmacokinetics of LCB01-0371 with Vancomycin versus Vancomycin standard therapy in patients with Methicillin Resistance Staphylococcus aureus (MRSA) Bacteremia

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Prepared by
C&R Research

Signature Page

C&R Research

Prepared by:

Ji Eun Park/BSPL	See eTMF Signature page.
Name/ Role	Signature/Date (DD-MMM-YYYY)

Reviewed by:

Ye Eun Kwon/BSR	See eTMF Signature page.
Name/ Role	Signature/Date (DD-MMM-YYYY)

Sponsor

Approved by Sponsor:

Seonghye Cheon/Project Manager	See eTMF Signature page.
Name/ Role	Signature/Date (DD-MMM-YYYY)
Yoon Hee Lee/Team Manager	See eTMF Signature page.
Name/ Role	Signature/Date (DD-MMM-YYYY)

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1.0	19-Jun-2024	Ji Eun Park	First Version
1.1	04-Jul-2024	Ji Eun Park	- [7.1 Handling of Missing Data] Addition of handling of missing data for subjects who have taken prohibited medications after the EOT. - [9.2.3 Relapse Rate of MRSA Bacteremia] Addition of verification methods for Day 3, Day 5, and Unscheduled time points.

Abbreviation

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC code	Anatomical Therapeutic Chemical code
ARS	All Randomized Set
BMD	Broth Microdilution
BMI	Body Mass Index
CS	Clinically Significant
DC	Discontinuation
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
ICH	International Council for Harmonization
ITT	Intention To Treat
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin Resistance Staphylococcus Aureus
NCS	Not Clinically Significant
OC	Observed Case
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	Treatment-Emergent Adverse Events
TOC	Test of Cure

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1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical analysis methods, data processing methods, and definitions of analysis sets for the final analysis of the study <LCB35-0371-21-2-01, Version 5.0, A multicenter, double blinded, randomized, parallel design, phase IIa clinical trial to evaluate the efficacy, safety and pharmacokinetics of LCB01-0371 with vancomycin versus vancomycin standard therapy in patients with methicillin resistance staphylococcus aureus (MRSA) bacteremia, 07 Dec 2022> based on ICH E9. The format and table of contents of the tables, figures, and listings in which the analysis results are recorded will be developed in a separate document.

If the analyses are performed using methods other than those described in this document, the modified methods and the reasons for the modifications will be detailed in the Clinical Study Report (CSR).

2. Study Objectives

2.1 Primary Objective

To compare the proportion of subjects with overall cure between LCB01-0371 plus vancomycin combination therapy and standard vancomycin therapy.

2.2 Secondary Objectives

To evaluate the following efficacy parameters of LCB01-0371 plus vancomycin combination therapy in subjects with MRSA bacteremia:

1) Proportion (%) of subjects with overall cure by the end-of-treatment (EOT) visit
2) Mortality due to MRSA bacteremia during the treatment period with the investigational product
3) Relapse rate of MRSA bacteremia
4) Proportion of subjects with two consecutive negative MRSA blood culture results on Day 3, Day 5, Day 7, Day 14 and at the EOT visit (clearance of MRSA bacteremia at Day 3, Day 5, Day 7, Day 14, EOT)
5) Proportion of subjects with persistent MRSA bacteremia based on blood culture results on Day 3, Day 5, Day 7, and Day 14
6) Time to clearance of MRSA bacteremia (in days)
7) Safety of the combination therapy with vancomycin and LCB01-0371
8) Pharmacokinetic (PK) profile of the combination therapy with vancomycin and LCB01-0371

3. Study Endpoints

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

Proportion of subjects with overall cure on Day 14 of treatment (composite response rate)

3.1.2 Secondary Efficacy Endpoints

1) Proportion of subjects with overall cure by the EOT visit (composite response rate)
2) Mortality due to MRSA bacteremia during the treatment period with the investigational product
3) Relapse rate of MRSA bacteremia
4) Proportion of subjects with two consecutive negative MRSA blood culture results on Day 3, Day 5, Day 7, Day 14 and at the EOT visit
5) Proportion of subjects with persistent MRSA bacteremia based on blood culture results on Day 3, Day 5, Day 7, and Day 14
6) Time to clearance of MRSA bacteremia (in days)

3.2 Safety Endpoints

1) Incidence and severity of treatment-emergent adverse events (TEAEs) and adverse drug reactions (ADRs) based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0)
2) Mortality due to exacerbation of MRSA bacteremia at the time of the TOC visit (4 weeks (28 days) after EOT) after starting treatment with the investigational product
3) Incidence (%) of thrombocytopenia
4) Vital signs
5) Electrocardiogram (ECG)
6) Laboratory tests
7) Abnormal changes in physical examination

3.3 PK Parameters

1) C_{max}
2) AUC_{last}
3) T_{max} (hr)
4) $T_{1/2}$ (hr)
5) CL

3.4 Other Parameters

1) MIC_{BMD}

4. Study Design

4.1 Summary

This clinical study is a phase 2a, multicenter, randomized, double-blind, parallel design study to evaluate the safety and efficacy of combination therapy with vancomycin and LCB01-0371 compared to standard vancomycin therapy in subjects with MRSA bacteremia.

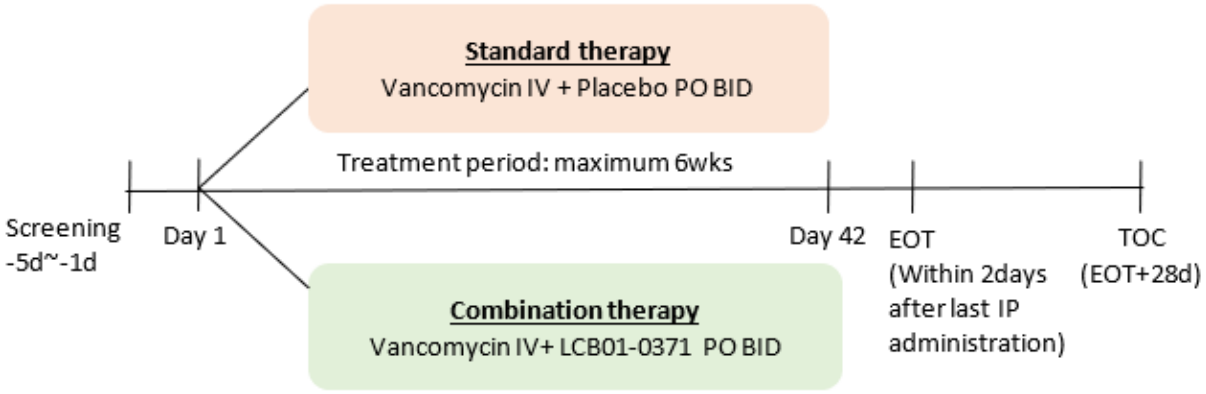

Figure 1 Study Schema

4.2 Rationale for Sample Size Determination

The purpose of this study is to evaluate the efficacy and safety of LCB01-0371 in combination with vancomycin compared to standard vancomycin therapy. Therefore, the number of subjects required for statistical hypothesis testing to ensure sufficient statistical power is not calculated. The target number of subjects is 100 (50 in the study group, 50 in the control group) who have received the investigational product.

4.3 Randomization Method

The randomization codes for this study were generated using SAS® (Version 9.4, SAS Institute Inc., Cary, NC, USA) by a statistician unrelated to this study, employing the block randomization method for each study site to ensure a 1:1 allocation ratio between treatment groups at each study site. Subsequently, subjects who meet the inclusion/exclusion criteria are assigned to each treatment group in order of enrollment using the randomization codes via Interactive Web Response System (IWRS).

5. Analysis Sets

- ✓ **Enrolled Set**

  The Enrolled Set consists of subjects who have signed the informed consent form.

✓ **All Randomized Set (ARS)**
The All Randomized Set (ARS) consists of subjects who were randomized into the study.

✓ **Safety Set**
The safety set consists of all subjects who have received at least one dose of the investigational product. For the safety analyses, subjects will be analyzed based on the treatment group to which they are actually administered.

✓ **Full Analysis Set (FAS)**
The FAS will include subjects who have received at least one dose of the investigational product after randomization and for whom at least one efficacy assessment result is available. In addition, subjects who violate the inclusion/exclusion criteria will be excluded from the FAS analysis. The FAS is analyzed based on the treatment group to which the subjects were randomized.

✓ **Per-Protocol Set (PPS)**
Among the FAS, the Per-Protocol Set (PPS) includes subjects who completed the study without major protocol deviations. The final PPS will be determined by blind data review. Protocol deviations (PD) that may lead to exclusion from the analysis sets are as follows and are defined in a separate document (SD 0406 A. Definition of Analysis Population).

- Violation of the inclusion/exclusion criteria
- Administration of prohibited medication
- Treatment compliance < 80%
- Randomization errors
- Errors in the administration of investigational products
- Other major protocol deviation*

  * Protocol deviations that are not included in the PPS as indicated in the PD Specification.

5.1 Errors in the Administration of Investigational Products

If a subject did not receive the investigational product according to the randomized treatment group, the analysis will be performed as follows:

- If a subject did not receive the investigational product according to the randomized treatment group for part of the study period, the safety assessment analysis will be performed based on the treatment group corresponding to the drug administered for more than 50% of the total treatment period. If no treatment group accounts for more than 50% of the total treatment period, the analysis will be conducted according to the randomized treatment group. The analysis of the efficacy assessment will be performed according to the randomized treatment group.

- If a subject did not receive the investigational product during the entire study period according to the randomized treatment group, the safety assessment analysis will be performed according to the actual treatment group, and the efficacy assessment analysis will be performed according to the randomized treatment group as per the Intention To Treat (ITT) principle.

6. Statistical Methods

6.1 Analysis Program

Statistical analyses will be performed using the SAS® Enterprise Guide (version 8.2 or higher) interface with 9.4 64bit (SAS Institute Inc., Cary, NC, USA.) or higher versions.

6.2 General Statistical Considerations

Continuous variables are presented with the number of subjects, mean, standard deviation, median, minimum, and maximum, while categorical variables are presented with frequency and percentage. In principle, all tests will be performed with a two-sided test at a significance level of 5%, unless otherwise specified.

Means and medians are presented with one significant figure more than the raw data, and standard deviations are presented with two significant figures more than the raw data. The minimum, maximum, MIC 50, and MIC 90 are presented with the same number of significant digits as the raw data. The percentages are given to two decimal places. However, if the number of significant digits exceeds four, they are rounded to four digits (rounded at the fifth decimal place). For derived variables (e.g., BMI), values up to two decimal places are treated as raw data for analysis.
The p-values are presented to four decimal places (rounded at the fifth decimal place). p-values less than 0.0001 are reported as <0.0001, and p-values greater than 0.9999 are reported as >0.9999.

All data used in the statistical analysis are presented in listings, and if there are missing data imputation, both the original data without imputation and the imputed data are presented.

6.3 Multicenter Study

This study does not conduct analyses by study site.

6.4 Subgroup Analysis

According to [9. Efficacy Analysis], the following subgroup analyses will be performed for the primary and secondary efficacy endpoints (overall cure and time to clearance of MRSA bacteremia), which will be restricted to the FAS.

- Subjects who are switched to daptomycin treatment

- Subjects who are switched to oral antibiotics after treatment with vancomycin (including switching to daptomycin)
- Administration of oral antibiotics (for MRSA) 14 days after administration of the investigational product
- Vancomycin high MIC (<1.5 vs >=1.5)
- Removal of the primary lesion
- Complication status (complicated vs. uncomplicated)
- Subjects who have received antiviral or antifungal medication during the study period

6.5 Multiple Comparison or Multiplicity of the Test

No multiple comparisons or multiplicity of tests will be performed in this study.

7. Data Processing Methods

7.1 Handling of Missing Data

All efficacy and safety endpoints will be analyzed using the observed case (OC) method without imputing missing data.

If a subject's visit date for an efficacy endpoint analysis is outside the planned visit window, the measurement for that visit will be treated as missing. In addition, for subjects who have received a contraindicated medication after the EOT visit that could affect efficacy, the measurement for the TOC visit will be treated as missing in the PPS analysis.

For laboratory tests, etc., the final visit measurement will be defined as the last measurement regardless of the planned visit window.

7.1.1 Censoring Rules

To evaluate the clearance of MRSA bacteremia, the reference date for the time of occurrence of the event will follow [Table 1].

Table 1 Censoring Rules

Scenario	Date of MRSA Clearance or Censoring	Outcome
If two consecutive negative results are confirmed, with the second test performed within three days of the first negative result	Date of the blood culture with the first negative result	Event occurred (event)
If two consecutive negative results are not confirmed	Date of completion/withdrawal	Censored
Withdrawal and follow-up loss	Date of completion/withdrawal	Censored

7.2 Handling of Missing Data for Date Variables

Any missing data for date variables will be imputed as follows.

Table 2 Handling of Missing Data for Date Variables

Missing Date	Missing Value	Imputation	Example
1. Start date of prior/concomitant medication 2. Start date of concomitant therapy	Year-Month-Day	[Year]-01-01 of the date of informed consent	Date of informed consent: 2021-12-05 Date collected: UK-UK-UK Imputed date: 2021-01-01
	Month-Day	01-01	Date collected: 2021-UK-UK Imputed date: 2021-01-01
	Day	01	Date collected: 2021-12-UK Imputed date: 2021-12-01
1. End date of prior/concomitant medication 2. End date of concomitant therapy	Year-Month-Day	Date of last visit	Date of last visit: 2021-12-25 Date collected: UK-UK-UK Imputed date: 2021-12-25
	Month-Day	12-31	Date collected: 2021-UK-UK Imputed date: 2021-12-31
	Day	Last [day] of month	Date collected: 2021-12-UK Imputed date: 2021-12-31
Onset date of adverse event	Year-Month-Day	Start date of the investigational product	Start date of administration: 2021-12-05 Date collected: UK-UK-UK Imputed date: 2021-12-05
	Month-Day	1. If [year] is the same as the start date of the investigational product: Use the [month-day] of the start date of the investigational product. 2. If [year] is different from the start date of the investigational product: 01-01	1. Start date of administration: 2021-12-05 Date collected: 2021-UK-UK Imputed date: 2021-12-05 2. Start date of administration: 2021-12-05 Date collected: 2022-UK-UK Imputed date: 2022-01-01
	Day	1. If [year-month] is the same as the start date of the investigational product: Use the [day] of the start date of the investigational product. 2. If [year-month] is different from the start date of the investigational product: Use 1.	1. Start date of administration: 2021-12-05 Date collected: 2021-12-UK Imputed date: 2021-12-05 2. Start date of administration: 2021-12-05 Date collected: 2022-05-UK Imputed date: 2022-05-01
AE end date	Year-Month-Day	Date of last visit	End date of administration: 2021-12-30 Date collected: UK-UK-UK Imputed date: 2021-12-30
	Month-Day	1. If [Year] is the same as the date of last visit: Use the [month-day] of the date of last visit. 2. If [Year] is different from the date of last visit: 12-31	1. End date of administration: 2021-12-30 Date collected: 2021-UK-UK Imputed date: 2021-12-30 2. End date of administration: 2021-12-30 Date collected: 2022-UK-UK Imputed date: 2022-12-31
	Day	1. If [year-month] is the same as the date of last visit: Use the [day] of the date of last visit.	1. End date of administration: 2021-12-30

Missing Date	Missing Value	Imputation	Example
			Date collected: 2021-12-UK Imputed date: 2021-12-30
		2. If [year-month] is different from the date of last visit: Last [day] of month	2. End date of administration: 2021-12-30 Date collected: 2021-05-UK Imputed date: 2021-05-31

7.3 Derived or Transformed Variables

Baseline values will be defined as the last measured values among those measured before or on the day of the first administration of the investigational product.

Table 3 Definition of Derived or Transformed Variables

Variable	Method
Change	Post-baseline measurement – Baseline measurement
BMI (kg/m^2)	$\frac{\text{Weight (kg)}}{\text{Height (m)}^2}$ Rounded to two decimal places (rounding at the third decimal place).
Age group	Age < 65 years, Age ≥ 65 years
Duration of adverse events (days)	Adverse event end date – Adverse event onset date + 1 If the adverse event end date is ongoing, it is replaced by the 'date of last visit' and indicated with ≥ (e.g., ≥ 15).
Time point of onset of adverse event (days)	Adverse event start date – Start date of the investigational product + 1
Switch to daptomycin treatment	Defined as cases where 'vancomycin' was administered first and then 'daptomycin,' based on the 'Drug Name (Generic Name)' on the CRF [Antibiotic Administration] page.
Switch to oral antibiotics after treatment with vancomycin (including switching to daptomycin)	Defined as cases where 'vancomycin' and 'daptomycin' were administered first and then 'oral antibiotic,' based on the 'Drug Name (Generic Name)' on the CRF [Antibiotic Administration] page.
Administration of oral antibiotics (for MRSA) 14 days after administration of the investigational product	Defined as cases in which the 'Drug Name (Generic Name)' on the CRF [Antibiotic Administration] page is an 'oral antibiotic,' 'Purpose of Administration' is 'Concomitant Medication for Investigational Product,' and the start date is 14 days after the first administration of the investigational product.
Vancomycin high MIC	Categorized as < 1.5 μg/mL or ≥ 1.5 μg/mL based on the minimum inhibitory concentration (MIC) at the time of screening. However, if the Local Lab value is higher than the Central Lab value, the Local Lab value will be used.
Feasibility of primary lesion removal	Defined as cases where the CRF [Primary Lesion] page indicates 'Yes' to the question 'Is the primary lesion removable?.'
Removal of the primary lesion	Defined as cases where the CRF [Primary Lesion] page indicates 'Yes' to both 'Is the primary lesion removable?' and 'Was the primary lesion removed?'

Variable	Method
Presence of complication	1) Defined as cases where the CRF [Past and Current Medical History] page records 'Yes' for 'Related to MRSA Bacteremia' and at least one of the following conditions is present: • Septic arthritis • Deep tissue abscess • Vertebral osteomyelitis • Epidural abscess • Septic thrombophlebitis • Psoas abscess • Meningitis • Mycotic aneurysm • empyema • pericarditis • pneumonia 2) or cases where CRF [Primary Lesion] page indicates 'infective endocarditis' as the primary lesion.
Antiviral or antifungal treatment during the study period	Defined as cases where there is a history of antiviral or antifungal treatment.

7.4 Definition of Analysis Visits

Subjects who discontinued the investigational product and were withdrawn from the study must conduct an end-of-treatment (EOT) visit. If the date of the EOT visit is within the planned visit period and no results are available for that visit, the results of the EOT visit will be considered the results of the scheduled visit and included in the analysis. If results are available for the corresponding visit, the results closer to the visit planned in the protocol will be considered results for that visit and included in the analysis. If the absolute values of the differences in visit dates based on the scheduled visit are identical (e.g., -3 days, +3 days), the previously measured results (-3 days) will be considered results for that visit and included in the analysis. In addition, the results of unscheduled visits will be analyzed in the same way.

All visit results, including unscheduled visits, will be shown in listings, regardless of whether they are within the allowed range of analysis visits.

Analysis visits are defined as follows. However, if there are variables with different visit dates and measurement dates (or test dates), the analysis will be based on the measurement date (or test date).

Table 4 Definition of Analysis Visits

Analysis Visit	Visit Day Interval (days)	Visit Window (days)	Allowed Range for Analysis Visit (days)
Screening (Visit 1)	-5		
Baseline (Visit 2)	1		
Visit 3	3		$3 \leq$ Visit 3-Baseline+1 ≤ 3
Visit 4	5		$5 \leq$ Visit 4-Baseline+1 ≤ 5
Visit 5	7	± 1	$6 \leq$ Visit 5-Baseline+1 ≤ 8
Visit 6	14	± 2	$12 \leq$ Visit 6-Baseline+1 ≤ 16
End of Treatment	-	$+ 2$	EOT/DC $\leq$ Date of the last dose of the

Analysis Visit	Visit Day Interval (days)	Visit Window (days)	Allowed Range for Analysis Visit (days)
(EOT)/DC			investigational product + 2
Test of Cure (TOC)	28	± 4	24 ≤ TOC-EOT+1 ≤ 32

7.5 Handling of Data Errors After DB Lock

If an error list is created after database (DB) lock, the related content will not be reflected in the analysis but will be noted in the annotations.

8. Subject Information

8.1 Subject Disposition

The frequency of the screening, screening failures, and reasons for the failure will be indicated. For subjects who were randomized, study completion status, reasons for withdrawal, and detailed reasons for treatment failure will be reported as frequencies and percentages for each treatment group and the total number. In addition, the frequencies of enrolled subjects per study site and subjects who were randomized, as well as the completion status of the study, will be reported as frequencies and percentages for each treatment group and the total number per study site. The analyses will be performed on the Enrolled Set or ARS, and the study participation status of subjects in the Enrolled Set will be presented in the listing.

8.2 Protocol Deviation

For each major protocol deviation, frequencies, percentages, and the number of occurrences for each treatment group and the total number will be presented. The analyses will be performed for the ARS, and protocol deviations for the ARS will be presented in the listing categorized as major/minor.

8.3 Analysis Set

For SS, FAS, and PPS, frequencies and percentages will be presented for each treatment group and the total number. Reasons for exclusion from each analysis set will be presented as frequencies and percentages for each treatment group and the total number. The analyses will be performed for the ARS, and the analysis sets of the study for the ARS will be presented in the listing.

8.4 Evaluation of Demographic Data and Baseline Characteristics

8.4.1 Demographic Data and Baseline Characteristics

For the following evaluation items, continuous variables will be presented as number of subjects, mean, standard deviation, median, minimum, and maximum for each treatment group and the total number. Categorical variables will be presented as frequencies and percentages for each treatment group and the total number. The analyses will be performed on the SS, and demographic and baseline data will be presented in listings for the ARS.

- Age (years), age group (less than 65 years, 65 years or older), gender, fertility status

- Height (cm), weight (kg), BMI (kg/m^2)
- Classification of primary lesion, feasibility of primary lesion removal, removal of primary focus
- Vancomycin MIC(<1.5 ug/mL, >=1.5 ug/mL)

8.4.2 Medical History/Current Medical Conditions

Past medical history is defined as cases where [Presence at Visit] is [No], and current medical conditions are defined as cases where [Presence at Visit] is [Yes].

For subjects with past medical history and current medical conditions, frequencies, percentages, and number of occurrences will be presented for each treatment group and total number of cases. They will be coded according to the System Organ Class (SOC) and Preferred Term (PT) of Medical Dictionary for Regulatory Activities (MedDRA) Latest Major Version and show frequencies, percentages, and number of occurrences by treatment group. For the frequency count, a subject will be counted as 1 person in each classification (subjects with a past medical history/current medical condition, SOC, PT), even if they have several past medical history/current medical conditions.

The MedDRA version will be noted in the tables and listings. The analyses will be performed on the SS, and the medical history/concomitant disease information for the ARS will be presented in the listing.

8.4.3 Prior/Concomitant Medication

Prior medication is defined as a medication started prior to the administration of the investigational product, and concomitant medication is defined as a medication started after the administration of the investigational product.

Classification of prior medications

- Administration start date < Start date of the investigational product

Classification of concomitant medications

- Administration start date ≥ Start date of the investigational product

In addition, missing values in the date variables will be processed according to [7.2 Handling of Missing Data for Date Variables] to classify the prior/concomitant medication.

For subjects with prior medications and concomitant medications, frequencies, percentages, and the number of occurrences for each treatment group and the total number will be presented. They will be coded according to level 1 (anatomical main group) and preferred name of the World Health Organization Drug Dictionary (WHO-DD) Latest version to show frequencies, percentages, and the number of occurrences for each treatment group and the total number. For the frequency count, a subject will be counted as 1 person in each classification (subjects with

prior/concomitant medication, level 1, preferred name), even if they have several prior/concomitant medications.

The WHO ATC index version will be noted in the tables and listings. The analyses will be performed on the SS, and the prior/concomitant medication information for the ARS will be presented in the listing.

8.4.4 Concomitant Therapy

Concomitant therapy is defined as non-drug treatment other than the investigational product from the time of administration of the investigational product until the end of the study.

For subjects with concomitant therapy, frequencies, percentages, and number of occurrences will be presented for each treatment group and total number of cases. They will be coded according to the System Organ Class (SOC) and Preferred Term (PT) of Medical Dictionary for Regulatory Activities (MedDRA) Latest Major Version and show frequencies, percentages, and number of occurrences. For the frequency count, a subject will be counted as 1 person in each classification (subjects with concomitant therapy, SOC, PT), even if they have several concomitant therapies.

The MedDRA version will be noted in the tables and listings. The analyses will be performed on the SS, and the concomitant therapy information for the ARS will be presented in the listing.

8.5 Treatment Compliance

For treatment compliance, the number of subjects, mean, standard deviation, median, minimum, and maximum for each treatment group and the total number will be presented. In addition, treatment compliance will be classified as less than 80% and 80% or more, and frequencies and percentages will be presented. The analyses will be performed on the FAS and the PPS, and the treatment compliance information for the SS will be presented in the listing.

$$\text{Overall treatment compliance (\%)} = \frac{\text{Total number of tablets actually taken (administered)}}{\text{Total number of tablets to be taken (administered)}} \times 100$$

9. Efficacy Analysis

The efficacy assessment will be primarily analyzed using the FAS, with additional analyses performed using the PPS. In addition, the listing will provide information on the primary efficacy endpoint and the secondary efficacy endpoints for the FAS.

9.1 Analysis of the Primary Efficacy Endpoint

9.1.1 Proportion (%) of Subjects with Overall Cure on Day 14 of Treatment

The number and percentage of subjects with overall cure on Day 14 of treatment will be presented with the

corresponding 95% confidence intervals by treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test.

Overall cure is defined as the disappearance of infection symptoms present at study enrollment, no new infections and/or secondary infections caused by MRSA (clinical improvement), and two consecutive negative MRSA blood cultures (clearance of MRSA bacteremia)*.

*If the first blood culture result is negative, a subsequent test will be performed within 3 days, and clearance of MRSA bacteremia will be established when two consecutive negative results are confirmed.

$$\text{Composite Response Rate (\%)} = \frac{\text{The number of subjects with overall cure on Day 14}}{\text{The number of subjects per group}} \times 100$$

9.2 Analysis of the Secondary Efficacy Endpoints

9.2.1 Proportion (%) of Subjects with Overall Cure by the EOT Visit

The number and percentage of subjects with overall cure at 7 days before the EOT visit and at the time of the EOT visit will be presented with the corresponding 95% confidence intervals by time point and treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test.

$$\text{Composite Response Rate(\%)} = \frac{\text{The number of subjects with overall cure at each time point}}{\text{The number of subjects per group}} \times 100$$

9.2.2 Mortality (%) due to MRSA Bacteremia During the Treatment Period with the Investigational Product

It is defined as the proportion of subjects who died from MRSA bacteremia during the treatment period after the start of the investigational product. The number and percentage of subjects who died during the treatment period after the start of the investigational product will be reported along with the 95% confidence interval for each treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test.

$$\text{Mortality due to MRSA bacteremia} = \frac{\text{The number of subjectswho died due to exacerbation of MRSA bacteremia during the treatment period}}{\text{The number of subjects per group}} \times 100$$

9.2.3 Relapse Rate of MRSA Bacteremia

The relapse rate of MRSA bacteremia is defined as the proportion of subjects with relapse of MRSA bacteremia

after two consecutive negative MRSA test results and within the TOC visit. The relapse of MRSA bacteremia refers to microbiological relapse, i.e., a positive MRSA in blood culture after two consecutive negative MRSA confirmations. The number and percentage of subjects with relapse of MRSA bacteremia will be presented with the corresponding 95% confidence intervals for each treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test. However, to confirm the denominator, the results collected on the [Blood Culture] page will be used for analysis at Day 3, Day 5, and unscheduled time points.

$$\text{Relapse Rate of MRSA Bacteremia} = \frac{\begin{array}{c}\text{The number of subjects with relapse MRSA bacteremia}\\ \text{after two consecutive negative MRSA test results}\\ \text{and prior to the TOC visit}\end{array}}{\begin{array}{c}\text{The number of subjects}\\ \text{with two consecutive negative MRSA test results per group}\end{array}} \times 100$$

9.2.4 Proportion of Subjects with Two Consecutive Negative MRSA Blood Culture Results on Day 3, Day 5, Day 7, Day 14 and at the EOT Visit

It is defined as the proportion of subjects who had two consecutive negative MRSA confirmations at each time point on Day 3, Day 5, Day 7, Day 14, and EOT*. The number and percentage of subjects with two consecutive negative MRSA confirmations will be presented along with the 95% confidence interval for each time point and treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test. However, for the analysis of Day 3 and Day 5, the results recorded on the [Blood Culture] page will be used.

* If two consecutive negative MRSA blood culture results are obtained prior to the EOT visit, these results can be considered as the blood culture results for the EOT visit.

$$\text{Clearance Rate} = \frac{\begin{array}{c}\text{The number of subjects}\\ \text{with two consecutive negative MRSA test results at each time point}\end{array}}{\text{The number of subjects at each time point}} \times 100$$

9.2.5 Proportion of Subjects with Persistent MRSA Bacteremia Based on Blood Culture Results on Day 3, Day 5, Day 7, and Day 14

It is defined as the proportion of subjects with positive MRSA blood cultures at each time point (Day 3, Day 5, Day 7, Day 14) after the first positive MRSA result (index blood culture) confirmed before randomization. The number and percentage of subjects with persistent MRSA bacteremia will be reported along with the 95% confidence interval for each time point and treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test. However, for the analysis of Day 3 and Day 5, the results recorded on the [Blood Culture] page will be used.

Proportion of subjects with persistent MRSA bacteremia

$$= \frac{\text{The number of subjects with persistent MRSA bacteremia at each time point}}{\text{The number of subjects at each time point}} \times 100$$

9.2.6 Time to Clearance of MRSA Bacteremia (in Days)

If the first negative blood culture result is confirmed, another test will be performed within 3 days. Clearance of MRSA bacteremia is confirmed by two consecutive negative results. The time to clearance of MRSA bacteremia is defined as the period (in days) from the date of the first MRSA-positive blood culture before randomization to the date of the first confirmed negative result in the blood culture.

Censoring is defined as cases where two consecutive negative results are not confirmed, and the censoring date follows the method in [7.1.1 Censoring Rules].

- Duration (days) = (date of clearance of MRSA bacteremia or censoring) – (date of first positive MRSA confirmation before randomization) + 1

After testing the proportional hazards assumption for differences between groups, the log-rank test will be performed if the assumption is met. If the proportional hazards assumption is not met, the generalized Wilcoxon test (Gehan test) will be performed using different weights from the weighted log-rank test family. The proportional hazards assumption will be tested using time-dependent log(-log S(t)) plots and a residual analysis (Cox-Snell method). If the cumulative hazard function of the Cox-Snell residuals is estimated and the dispersion of the residuals appears as a straight line with a slope of 1, it can be assumed that the assumption is fulfilled. Survival curves and medians with corresponding two-sided 95% confidence intervals for each group will be presented using the Kaplan-Meier method, and estimates of hazard ratios with two-sided 95% confidence intervals will be provided using a Cox regression model with the treatment group as a covariate.

In addition, the time to clearance of MRSA bacteremia will be presented using the status of complication and the presence/absence of primary lesion as covariates.

The log-rank test will be performed if the proportional hazards assumption is met. If the proportional hazards assumption is not met, the generalized Wilcoxon test (Gehan test) will be performed. Survival curves and medians with corresponding two-sided 95% confidence intervals for each group will be presented using the Kaplan-Meier method, and estimates of hazard ratios with two-sided 95% confidence intervals will be provided using a Cox regression model.

10. Safety Analysis

The safety analyses will be performed for the SS.

10.1 Extent of Exposure

The number of subjects, mean, standard deviation, median, minimum and maximum for each treatment group will be reported for the total treatment period (days) and the total administered dose (mg) of the investigational product (LCB01-0371). In addition, exposure information for the SS will be presented in the listing.

Each endpoint is defined as follows.

- Total treatment period (days): Date of the last administration – date of the first administration + 1
- Total administered dose (mg): Number of the tablets of the investigational product administered X 400 mg

10.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event that either occurs after the administration of the investigational product or represents an exacerbation of a pre-existing condition after the administration of the investigational product. TEAEs will be classified by date of occurrence as follows:

- TEAE:
  Start date of the investigational product ≤ Date of occurrence of the adverse event

An adverse drug reaction (ADR) refers to a harmful and unintended reaction that occurs at any dose of an investigational product and for which the causal relationship with the investigational product cannot be excluded. An ADR is defined as an AE for which causal relationship to the investigational product is assessed as one of the following by the investigator.

- Definitely
- Probable/Likely
- Possible
- Unassessable

A serious adverse event (SAE) refers to any of the following AEs that occur at any dose of the investigational product.

- Results in death or is life-threatening
- Requires hospitalization or prolonged hospitalization

- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- In addition to cases above, cases where other important medical events occur, such as development of drug dependence or drug abuse, or hematological disease, etc.

10.2.1 Summary of Adverse Events

The following AEs will be reported with the number of subjects with occurrence, incidences, number of cases by treatment group, and the 95% confidence intervals for incidence. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test. Adverse event information for the SS will also be presented in listings.

- Treatment-emergent adverse events (TEAEs)
- Adverse drug reactions (ADRs)
- Serious adverse events (SAEs)
- Serious adverse drug reactions (SADRs)
- AEs leading to treatment discontinuation

10.2.2 Analysis of Adverse Events

The following AEs will be coded according to the latest version of MedDRA SOC and PT, and the number of subjects, incidences, and number of cases by treatment group will be reported. The MedDRA version will be noted in the tables and listings.

- Treatment-emergent adverse events (TEAEs)
- Adverse drug reactions (ADRs)
- Serious adverse events (SAEs)
- Serious adverse drug reactions (SADRs)
- AEs leading to treatment discontinuation
- TEAEs by severity
- ADRs by severity

AE information for the SS will also be presented in listings, and SAEs will be presented in separate listings.

10.3 Mortality due to Exacerbation of MRSA Bacteremia at the Time of the TOC Visit (4 Weeks after EOT) After Starting Treatment with the Investigational Product

The number and percentage of subjects who die due to exacerbation of MRSA bacteremia from the start of treatment with the investigational product to the TOC visit will be presented with the corresponding two-sided 95%

confidence intervals for each treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test.

$$\text{Mortality due to exacerbation of MRSA bacteremia at the time of the TOC visit} = \frac{\text{The number of subjects who died after administration of the investigational product up to the TOC visit}}{\text{The number of subjects per group}} \times 100$$

10.4 Incidence of Thrombocytopenia

The number and percentage of subjects who experience thrombocytopenia after administration of the investigational product will be presented with the corresponding two-sided 95% confidence intervals for each treatment group. Differences in proportions between groups will be tested using the chi-square test or Fisher's exact test.

$$\text{Incidence of thrombocytopenia} = \frac{\text{The number of subjects who experience thrombocytopenia after administration of the investigational product}}{\text{The number of subjects per group}} \times 100$$

10.5 Laboratory Tests

If the units of laboratory tests differ by study site, they will be standardized to the most commonly used unit for each item. Results with inequality signs will be analyzed as their numeric value.
e.g., < 1.002 will be analyzed as 1.002.

For continuous variables, the mean, standard deviation, median, minimum, and maximum for each treatment group will be provided for each measurement at different time points, measurements at the final visit, and changes from baseline.

Test results will be classified as normal/abnormal (NCS: not clinically significant; CS: clinically significant) and presented in shift tables with frequencies and percentages of change from baseline at each time point and at the final visit. The results will be further classified as low (< lower limit), normal (within the reference range), and high (> upper limit) and presented in shift tables with frequencies and percentages of change from baseline at each time point and at the final visit.

For categorical variables, test results will be classified as normal/abnormal (NCS, CS) and presented in shift tables with frequencies and percentages of change from baseline at each time point and at the final visit.

Laboratory test data for the SS will also be presented in listings, with all abnormal CS results after baseline provided in separate listings for each time point.

10.6 Vital Signs

For the following vital signs, the mean, standard deviation, median, minimum, and maximum for each treatment group will be provided for each measurement at different time points, measurements at the final visit, and changes from baseline. Vital sign information for the SS will also be presented in listings.

- Vital signs: Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (bpm), temperature (℃), respiratory rate (breaths per minute)

10.7 12-lead ECG

The test results will be classified as normal/abnormal (NCS, CS) and presented in shift tables with frequencies and percentages of change from baseline at the final visit. 12-Lead ECG information for the SS will also be presented in listings.

10.8 Physical Examination

For the SS, clinically significant abnormal findings in physical examination will be presented in the listing.

10.9 Pregnancy Test

For the SS, information on the pregnancy tests performed at each time point will be presented in the listing.

11. PK Analysis

11.1 PK Parameters

PK analysis will be performed at a designated analysis institution according to a separate PK analysis plan.

11.2 Other Parameters - MIC Evaluation

11.2.1 Evaluation of the MIC of Vancomycin

The following MICs at baseline will be reported with mean, standard deviation, median, minimum, maximum, MIC50*, and MIC90** for each treatment group. The analysis will be performed using the SS, and the vancomycin MIC evaluation data for the ARS will be presented in a listing.

*This refers to the value corresponding to the n × 0.5th position in the ordered list of MIC values. If n × 0.5 is not an integer, it is rounded up to the first decimal place.

**This refers to the value corresponding to the n × 0.9th position in the ordered list of MIC values. If n × 0.9 is not an integer, it is rounded up to the first decimal place.

- Vancomycin MIC evaluation: Minimum inhibitory concentration (mcg/mL)

Evaluation of the MIC of vancomycin will be performed at screening and when deemed necessary by the investigator. The analysis will be performed at the study site. In addition, MIC_{BMD} analysis can be performed at a designated laboratory by transferring samples when necessary.

11.2.2 Evaluation of the MIC of LCB01-0371

The following MICs will be presented for each treatment group at baseline and at the final visit. The changes from baseline at each time point and at the final visit will also be reported, including the number of subjects in each treatment group, mean, standard deviation, median, minimum, maximum, MIC50*, and MIC90**.

In addition, the measurements will be classified according to whether they increase 3-fold or more from baseline, and the corresponding frequency and percentage for each treatment group at each time point and at the final visit will be reported. The analysis will be performed using the SS, and the LCB01-0371 MIC evaluation data for the ARS will be presented in a listing.

*This refers to the value corresponding to the n × 0.5th position in the ordered list of MIC values. If n × 0.5 is not an integer, it is rounded up to the first decimal place.

**This refers to the value corresponding to the n × 0.9th position in the ordered list of MIC values. If n × 0.9 is not an integer, it is rounded up to the first decimal place.

- Evaluation of the MIC of LCB01-0371: Minimum inhibitory concentration (mcg/mL)

Evaluation of the MIC of LCB01-0371 will be performed at the time points specified when feasible, and the analysis will be performed separately at a designated analysis institution.

12. Interim Analysis

Not applicable.

13. Changes to the Planned Analysis Methods

Subgroups not defined in Section 11.2.6 Subgroup Analysis of the protocol were added (administration of oral antibiotics (for MRSA) after 14 days of the investigational product administration, vancomycin high MIC, removal of primary lesion, presence of complications).

Although no covariate adjustment was planned in the protocol, it was additionally changed to present the results adjusted for covariates (presence of complications and removal of primary lesion) for the secondary efficacy endpoint ‘time to clearance of MRSA bacteremia.’

14. SAS Program Code

The SAS program codes used for the statistical analysis in this study are as follows.

Table 5 SAS Program Code

Analysis Method	SAS program code
Descriptive statistics (mean, standard deviation, media, minimum, maximum)	PROC MEANS DATA= dataset N MEAN STD MEDIAN MIN MAX; VAR variable; RUN;
Descriptive statistics (frequency, percentage)	PROC FREQ DATA= dataset; TABLE variable; RUN;
Chi-square test Fisher's exact test	PROC FREQ DATA=dataset; TABLE variable*treatment/CHISQ EXACT FISHER; RUN;
Proportional Hazard Model	PROC PHREG DATA = dataset; CLASS treatment; MODEL time*event(0) = treatment (covariate) / risklimits; RUN;
Log-rank test	PROC LIFETEST DATA=dataset PLOTS=(survival logsurv) graphics METHOD=KM ALPHAQT=0.05; TIME time*event(0); STRATA treatment/test=logrank (or wilcoxon); RUN;

15. References

Not applicable.