Study Protocol

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

Investigational Product:	LCB01-0371
Protocol No.:	LCB35-0371-21-2-01
Protocol Version:	5.0
Phase of Development:	Phase 2a
Sponsor:	LegoChem Biosciences, Inc.
Date of Protocol Preparation:	2022-12-07

Confidentiality Statement

※ List of Abbreviations and Definition of Terms

ADR	adverse drug reaction
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve
AUC_{last}	area under the concentration-time curve from time 0 to the last measured time point
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
BID	twice daily
BMD	broth microdilution
BMI	body mass index
BUN	blood urea nitrogen
Ca	calcium
CA-MRSA	community-associated methicillin resistance *Staphylococcus aureus*
CFR	code of federal regulations
CFU	colony-forming unit
CIOMS	council for international organizations of medical sciences
Cl	chloride
CL	clearance
C_{max}	maximum serum concentration
CPK	creatine phosphokinase
CRO	contract research organization
CRP	c-reactive protein
CS	clinically significant
CYP	cytochrome p450
DBL	database lock
DC	discontinuation
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
FAS	full analysis set
hCG	human chorionic gonadotropin

HCT	hematocrit
hERG	human ether-à-go-go related gene
HRZE	ampicin, isoniazid, pyrazinamide, ethambutol
hVISA	heterogenous vancomycin intermediate s. aureus
ICF	informed consent form
ICH	international council for harmonization
IDMC	independent data monitoring committees
IDSA	infectious diseases society of America
INR	international normalized ratio
IRB	institutional review board
ITT	intention to treat
IUD	intrauterine system
IV	Intravenous
IWRS	interactive web-based response system
K	Potassium
KGCP	Korea good clinical practice
LOAEL	lowest observed adverse effect level
MCH	mean corpuscular hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
MIC	minimum inhibitory concentration
MAO	monoamine oxidase
MRSA	methicillin resistance *staphylococcus aureus*
MSSA	methicillin-susceptible *staphylococcus aureus*
MTD	maximum tolerated dose
Na	sodium
NCI-CTCAE	national cancer institute-common terminology criteria for adverse events
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
P	phosphorus
P.O.	per oral
PK	pharmacokinetics
PPS	per protocol set
PT	prothrombin time
PT	preferred term
RBC	red blood cell
rRNA	ribosomal ribonucleic acid
SAE	serious adverse event

S.aureus	Staphylococcus aureus
S.C.	subcutaneous
SAS	statistical analysis system
SOC	system organ class
SOP	standard operating procedure
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse events
T_{lag}	absorption delay
T_{max}	time to maximum concentration
TB	tuberculosis
TOC	test of cure
$T_{1/2}$	terminal half-life
V_d	volume of distribution
VISA	vancomycin-intermediate *Staphylococcus aureus*
VRSA	vancomycin-resistant *Staphylococcus aureus*
WBC	white blood cell
γ-GT	gamma-glutamyltransferase

Table of Contents

1 Study Title, Phase of Development, Protocol Identification Number, and Revision History

1.1 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

1.2 Phase of Development

Phase 2a study

1.3 Protocol Identification Number and Revision History

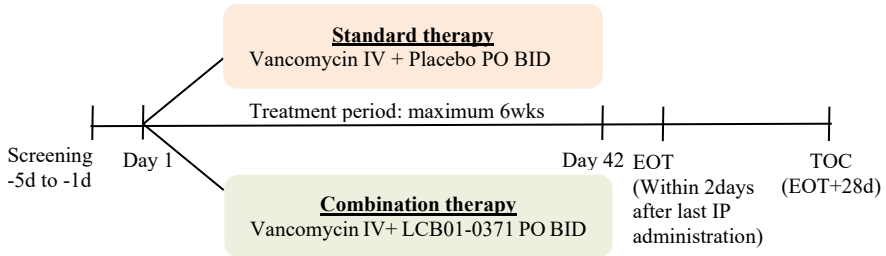
- Protocol identification No.: LCB35-0371-21-2-01
- Revision history

Version	Date	Comment
1.0	2021-06-11	• Initial version
1.1	2021-12-23	• Change of the MIC measurement of LCB01-0371 to optional. • Addition of details regarding instruction and evaluation of the treatment compliance. • Change in criteria for assessing causality of adverse events (reclassified “unlikely related” to “unrelated”) - applied relevant regulations. • Clarification of the criteria for the minimum administration period for the investigational product (at least 2 weeks). • Correction of typos and inconsistencies.
1.2	2022-02-04	• Changed PK blood sampling time (8h-12h >> 2h-8h). • Changed to allow vancomycin MIC_{BMD} to be performed in an additional analysis institution if required. • Correction of typos and clarification of phrases.
2.0	2022-04-13	• Clarification of descriptions for blood cultures [10.1.10] and laboratory tests [10.1.8]. • Correction of typos.
3.0	2022-07-06	• Changed the MRSA confirmation time before randomization (within 72 hours >> 96 hours) and the time window for empirical antibiotic use [reason: As this study is an exploratory Phase 2a study, the inclusion criteria were adjusted to allow for cases where blood culture for MRSA confirmation may exceed 72 hours]. • Addition of visit window during the treatment period. • Integration of Day 0 (baseline) and Day 1 (start of IP administration). • Clarification of phrases regarding two consecutive MRSA-negative confirmations. • Change of the schedule for body weight measurement and laboratory tests. • Addition of collection of information on the removal of primary MRSA lesion.
4.0	2022-11-21	• Change to the prohibited concomitant medications (allowed a switch to oral antibiotics, except for the oxazolidinones, based on investigator judgment after at least 14 days of vancomycin administration (including a switch to daptomycin)). • Addition of subgroup analysis (subjects switched to oral antibiotics after administration of vancomycin (including a switch to daptomycin)). • Correction of typos in the schedule of activities.
5.0	2022-12-07	• Exclusion criterion 2) Adjustment of the exclusion criterion for reinfection “Subjects who have received treatment within the last 3 months”.

2 Synopsis

Study Title	A Multicenter, Double blinded, Randomized, Parallel Design, Phase 2a 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
Phase and Design	Multicenter, double-blind, randomized, parallel design, Phase 2a study (proof of concept)
Study Site	See Attachment 3. List of Study Sites and Investigators.
Sponsor	LegoChem Biosciences, Inc.
Study Objectives	To evaluate the efficacy of the combination therapy of LCB01-0371 and vancomycin compared to standard vancomycin therapy in subjects with methicillin-resistant Staphylococcus aureus (MRSA) bacteremia and to investigate its safety and pharmacokinetic profile. **[Primary Objective]** To compare the proportion of subjects with overall cure between LCB01-0371 plus vancomycin combination therapy and standard vancomycin therapy. **[Secondary Objectives]** 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 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) 7) Safety of the combination therapy with vancomycin and LCB01-0371 8) Pharmacokinetic (PK) profile of the combination therapy with vancomycin and LCB01-0371
Target Population	Patients with MRSA bacteremia
Inclusion Criteria	1) Male or female subjects ≥19 years of age at the time of written consent 2) Subjects in whom at least one set of blood cultures tested positive for MRSA within 72 hours prior to randomization; or subjects in whom at least one set of blood cultures tested positive for MRSA within 96 hours prior to randomization and who started treatment with vancomycin at least 72 hours prior to randomization 3) Subjects who have clinical symptoms or signs of MRSA bacteremia according to the judgment of the investigator 4) Subjects who have voluntarily decided to participate in this clinical study after being fully informed and who have agreed in writing to comply with the study requirements
Exclusion Criteria	**Concurrent diseases and medical history** 1) Subjects with polymicrobial bacteremia, including Gram-negative bacteria, or infections 2) Subjects who have received treatment within the last 3 months (however, subjects may be enrolled if they have reinfection as determined by the investigator, regardless of prior treatment within 3 months) 3) Subjects who had received empirical antibiotics for more than 96 hours prior to randomization (limited to 72 hours for MRSA-active antibiotics such as vancomycin) 4) Subjects with septic shock

	5) Subjects with hypersensitivity to vancomycin or linezolid 6) Subjects infected with bacteria that are resistant to vancomycin or linezolid 7) Subjects with a history of hypersensitivity to peptide antibiotics or aminoglycosides 8) Subjects who are currently receiving or have received monoamine oxidase (MAO) inhibitors within 14 days prior to the first administration of the investigational product 9) Subjects who are currently receiving serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone 10) Subjects who are severely immunocompromised (e.g., severe neutropenia (absolute neutrophil count (ANC) $<0.5\times10^9$/L)) 11) Subjects who, in the opinion of the investigator, are expected to die within 2 days from the severe complications of MRSA bacteremia **Other** 12) Body Mass Index (BMI) ≥35 kg/m^2 13) Subjects who are unable to administer medication orally 14) Pregnant or lactating subjects or women and men of childbearing potential who are unwilling to use appropriate contraceptive methods* during the study period and for 14 days after the last administration of the investigational product. * Contraceptive methods: Use of at least one barrier method (e.g., implants, injections, oral contraceptives, intrauterine devices (IUDs)) in combination with hormonal IUDs, absolute abstinence, or vasectomy (subjects must consent to the use of at least two contraceptive methods). However, periodic abstinence (e.g., ovulation cycle, symptothermal, or post-ovulation methods) and withdrawal are not considered acceptable methods of contraception. 15) Subjects who have received other investigational products within 30 days prior to screening 16) Other subjects who, in the medical judgment of the investigator, are not suitable for participation in this study
Target Number of Subjects	• 100 subjects in total (50 subjects per group) Treatment group — Number of Subjects Vancomycin IV + LCB01-0371 P.O. BID — 50 subjects Vancomycin IV + Placebo P.O. BID (matching LCB01-0371) — 50 subjects
Study Period	• Total study period: 24 months from the date of the IRB approval (subject to change depending on subject enrollment rates). • Duration for each subject: Up to 75 days ➢ Screening period: Up to 5 days ➢ Treatment period: Up to 42 days (at least 14 days) • Treatment evaluation period: 28 days
Investigational Product and Concomitant Medication	1) LCB01-0371 (Delpazolid) 2) Placebo of LCB01-0371: A matching placebo that has the same formulation and appearance as LCB01-0371 3) Concomitant medication: Vancomycin
Dosage, Treatment Period, and Administration Method	1) **Treatment Period:** Up to 42 days (at least 14 days) 2) **Dosage and Administration Method** ① LCB01-0371 or placebo: 2 tablets per dose, administered orally twice daily (morning and evening) ② Vancomycin: Initial dose of 15-20 mg/kg, administered intravenously q8h-q12h (assuming MIC_{BMD} = 1 mcg/mL), with subsequent dose adjustments to maintain the vancomycin concentration at an AUC/MIC_{BMD} ratio of 400-600 [see 2020 Infectious Diseases Society of

	America (IDSA) guidelines]. • The investigator can adjust the vancomycin dosage and treatment regimen based on the subject's renal function according to the approved vancomycin labeling and therapeutic drug monitoring (TDM) results.
Study Methodology	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. Subjects will voluntarily provide written consent to participate in this study, and screening tests and procedures will be performed. Subjects who have started empirical antibiotic therapy within 96 hours prior to randomization (limited to 72 hours for MRSA-active antibiotics such as vancomycin) and who have at least one positive MRSA blood culture and meet the inclusion and exclusion criteria will be enrolled in the study. Subjects will then be randomized in a 1:1 ratio to either the study group (LCB01-0371 and vancomycin combination) or the control group (standard vancomycin therapy [placebo of LCB01-0371 and vancomycin combination]). The randomized subjects can receive the investigational product according to their assigned group for up to 42 days (at least 14 days). If the investigator determines that a switch to an antibiotic other than vancomycin is necessary for the treatment of MRSA bacteremia after initiation of therapy, a switch to daptomycin is allowed. After at least 14 days of vancomycin therapy (including switching to daptomycin), an oral antibiotic (excluding oxazolidinones) can be administered at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits. As the subjects are hospitalized, they will undergo scheduled examinations and procedures, including pharmacokinetic assessments, at each time point. Upon completion of the administration of the investigational product, subjects will attend the EOT and test of cure (TOC) visits for tests and procedures to evaluate efficacy and safety. 
Withdrawal Criteria	① Voluntary withdrawal of consent by the subject. ② When it is judged by the investigator that it is difficult to conduct further clinical trials due to adverse reactions and adverse drug reactions ③ When the subject's condition is deteriorating and the investigator determines that it is difficult to conduct further clinical trials (shock, cardiopulmonary resuscitation, ventilator treatment, etc.) ④ If the following treatment failure criteria are met during treatment period - The investigator determines that a switch to another antibiotic for the treatment of MRSA bacteremia is required after at least 7 days of vancomycin administration (however, if vancomycin was deemed ineffective during the administration period, a switch to daptomycin was allowed at the discretion of the investigator. After at least 14 days of vancomycin therapy (including switching to daptomycin), an oral antibiotic (excluding oxazolidinones) may be administered at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue

	scheduled visits.) - New infections other than MRSA or secondary infections resulting from MRSA bacteremia requiring treatment are identified after the first administration of the investigational product. - Confirmed decreased susceptibility to vancomycin. ⑤ When the pregnancy of the subject is confirmed during administration of the clinical investigational drug ⑥ When investigators decide that the subject should stop participating in the trial for other reasons
Permitted Concomitant Medications and Treatments	The following medications are allowed during the study period: 1) Medications other than contraindicated combinations may be administered during the study (from the first administration of the investigational product to the completion of the TOC visit, as specified in the protocol) at the discretion of the investigator, provided the dosage remains stable. 2) Temporary medications and treatments for symptom control due to MRSA bacteremia are allowed, except for antibiotics specifically used to treat MRSA bacteremia. 3) Daptomycin: After at least 7 days of vancomycin administration, subjects can be switched to daptomycin if deemed necessary by the investigator for the treatment of MRSA bacteremia. Subjects who discontinue vancomycin and are switched to daptomycin (6–10 mg/kg, q24h h, IV) will continue scheduled visits. The investigator may adjust the dosage and administration of daptomycin according to the approved labeling based on the subject's renal function. 4) After at least 14 days of treatment with vancomycin (including switching to daptomycin), subjects may be switched to oral antibiotics other than oxazolidinones at the discretion of the investigator and continue scheduled visits. 5) Temporary administration of antibiotics for skin and soft tissue infections or urinary tract infections is allowed at the discretion of the investigator (however, linezolid and tigecycline are prohibited during the study). 6) Antiviral and antifungal agents used for prophylaxis may be administered concomitantly at the discretion of the investigator. 7) Medications for the temporary treatment of other diseases may be administered concomitantly after consultation with the investigator. If any concomitant medications (including medications to treat other diseases or adverse events [AEs]) are administered, the investigator should record the information about the medications (product name, purpose of administration, dose, treatment period, etc.) in detail in the electronic case report form (eCRF).
Prohibited Medications and Treatments	The following medications are prohibited throughout the study: 1) Antibiotics with antibacterial activity against MRSA (e.g., rifampin, clindamycin, trimethoprim-sulfamethoxazole, doxycycline, gentamicin, linezolid, tigecycline, etc.). However, empirical antibiotics, including vancomycin, used to treat Gram-positive bacteria within 72 hours prior to administration of the investigational product are allowed. In addition, after at least 14 days of treatment with vancomycin (including switching to daptomycin), subjects may be switched to oral antibiotics other than oxazolidinones at the discretion of the investigator. 2) MAO inhibitors (drugs that inhibit MAO-A or MAO-B; e.g., phenelzine, isocarboxazid, selegiline, moclobemide, etc.) 3) Selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), meperidine, buspirone
Medications to be Used with Caution	The following medications may be administered concomitantly during the study, but must be closely monitored due to possible interactions with vancomycin. 1) Medications with potential neurotoxicity or nephrotoxicity (e.g., amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, platinum-containing anticancer drugs (cisplatin, nedaplatin, etc.)) 2) Anticoagulants

Endpoints

(1) Efficacy Endpoints

1) Primary endpoint

- Proportion of subjects with overall cure on Day 14 of treatment (composite response rate)
  : "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)[a].
  [a.] If the first blood culture result is negative, a subsequent test will be performed within 3 days, and clearance of MRSA bacteremia is established when two consecutive negative results are confirmed.

2) Secondary 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
: Proportion of subjects with relapse MRSA bacteremia after two consecutive negative MRSA test results and prior to the TOC visit

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 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)
: 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.

Definition of Clinical Outcome	
Clinical improvement	Disappearance of the symptoms of infection existing at the time of enrollment in the study, without new infections or new secondary infections caused by MRSA.
Clinical failure	Subjects who experience clinical failure during the treatment period will be considered treatment failures for the remainder of the study. The following cases are classified as clinical failure if any of the following criteria are met. ✓ Death due to MRSA bacteremia during the treatment period with the investigational product ✓ A switch to another antibiotic for the treatment of MRSA bacteremia is required (however, if the treatment with vancomycin fails during the treatment period, a switch to daptomycin is allowed at the discretion of the investigator. After at least 14 days of vancomycin administration (including switching to daptomycin), it can be switched to an oral antibiotic (excluding oxazolidinones) at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.) ✓ New infections other than MRSA or secondary infections resulting from MRSA bacteremia requiring treatment are identified.
Definition of Microbiological Outcome	

	<table><tr><td>Clearance of MRSA bacteremia</td><td>Two consecutive negative MRSA blood cultures.</td></tr><tr><td>Persistent MRSA bacteremia</td><td>Persistent MRSA positivity in blood cultures.</td></tr><tr><td>MRSA bacteremia relapse</td><td>Relapse of MRSA bacteremia after two consecutive negative MRSA test results and before the TOC visit</td></tr></table> **(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 after EOT) after starting treatment with the investigational product ③ Incidence (%) of thrombocytopenia ④ Abnormal changes in vital signs, electrocardiogram (ECG), laboratory tests, and physical examination **(3) Pharmacokinetic (PK) Assessments and Measurement of Minimal Inhibitory Concentration (MIC)** ① PK assessments • The time points of blood sampling and the PK parameters are as follows. <table><tr><td>Time points of blood sampling</td><td>Day 1: 30min-1h, 2h-8h After reaching steady state (from Day 3 to EOT): 30 min-1 h, 2-8 h</td></tr><tr><td>Endpoints</td><td>C_{max}, AUC_{last}, T_{max} (hr), $T_{1/2}$ (hr), clearance (CL), etc.</td></tr></table> ② Minimal Inhibitory Concentration (MIC) The MIC of vancomycin will be measured at the time of screening and at other time points as needed at the investigator's discretion to adjust the vancomycin dose. In addition, MIC_{BMD} analysis can be performed at a designated laboratory by transferring samples when necessary. The MIC of LCB01-0371 will be measured at the time of screening and analyzed up to Day 14 in subjects whose blood culture results are not negative conversion by Day 14. In subjects who discontinue treatment before Day 14 or whose blood cultures are not negative conversion by the EOT visit, the MIC of LCB01-0371 will be evaluated at the EOT visit. However, this evaluation will be performed only when possible and analysis of MIC of LCB01-0371 will be conducted at a designated laboratory.
Statistical Analysis Method	**(1) Efficacy Assessment Methods** **1) Primary Endpoint** • Proportion of subjects with overall cure on Day 14 of treatment (composite response rate) : The number and percentage of subjects 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. **2) Secondary 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: Proportion of subjects with relapse MRSA bacteremia after two consecutive negative MRSA test results and prior to the TOC visit 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 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

: The analysis methods for the endpoints ① - ⑤ are the same as for the primary endpoint.

⑥ Time to clearance of MRSA bacteremia (in days)

: 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). 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.

(2) Safety Assessment Methods

1) Incidence and severity of TEAEs and ADRs

All adverse events will be coded by using the latest version of the medical dictionary for regulatory activities (MedDRA).

The number of subjects, incidences (%), and number of cases of TEAEs and ADRs will be presented by treatment group, as well as the two-sided 95% confidence intervals for the incidences. AEs will be categorized and summarized as those related to the investigational product and those not related to the investigational product (such as concomitant medications and therapies, MRSA bacteremia, underlying diseases other than MRSA, none, unknown, or other related AEs).

In addition, the number of subjects, incidences, and number of cases of TEAEs and ADRs that occur in each treatment group will be presented by system organ class (SOC) and preferred term (PT).

2) 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.

3) 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.

4) Abnormal changes in vital signs, ECG, and physical examination

For continuous data such as vital signs, electrocardiogram, and laboratory tests (hematology and blood chemistry), descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for the measured value and the change from baseline at each visit. The results of laboratory tests and ECGs classified as normal, non-clinically significant (NCS) abnormal, or clinically significant (CS) abnormal will be summarized for subjects who exhibit CS abnormal results after treatment with the investigational product. Subjects who are classified as normal or NCS abnormal before administration of the investigational product but change to CS abnormal after administration of the investigational product will be listed separately. Subjects with abnormal CS

	findings on physical examination will also be listed. **(3) Assessment Methods for PK Parameters and MIC** 1) PK parameters include C_{max}, AUC_{last}, T_{max} (hr), $T_{1/2}$ (hr), CL, etc., which will be analyzed by a separate institution and presented descriptively based on the data structure. The report on the results of the PK assessment can be presented separately from the clinical study report. 2) MIC: Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided for MIC measurements.

※ Schedule of Activities

Period	Screening[#]	Treatment Period						End of Treatment (EOT)/DC[18]	Test of Cure (TOC)[18]
Visit day	**-5d ~**	**Day 1[#] (Baseline)**	**Day 3**	**Day 5**	**Day 7**	**Day 14**	**Day 15-42**	**-**	**EOT + 28 days**
Window period	-	-	-	-	±1d	±2d	±2d	+2d	±4d
Written informed consent[1]	●								
Review of the inclusion/exclusion criteria	●	●**							
Demographic data[2]	●								
Medical history and current medical conditions[3]	●	●*							
Prior medications[4]	●	●*							
Vital signs[5]	●	●*	●	●	●	●	Weekly (until discharge)	●	●
Body measurement[6]	●							●	
Physical examination[7]	●	●*	●	●	●	●	Weekly (until discharge)	●	●
Laboratory tests[8]	●	●*	(●)	(●)	●	●	Weekly (until discharge)	●	
12-lead ECG[9]	●							●	
Randomization		●*							
Blood cultures[10]	●	(●*)	●	●	●	●	(●)	●	
Vancomycin MIC evaluation[11]	●								
LCB01-0371 MIC evaluation (optional)[11]	●					●		●	
Efficacy assessment[12]			●	●	●	●		●	●
PK assessment[13]		●	One time between Day 3 and EOT						
Administration of the investigational product[14]		Daily (For at least Day 14 and up to Day 42)							
Administration of vancomycin[14]		Daily (up to 42 days)							
Concomitant medication/combination therapy[15]		●	●	●	●	●	●	●	●
Symptoms and signs of MRSA bacteremia[16]	●	●	●	●	●	●	●	●	●
AEs[17]		●	●	●	●	●	●	●	●

* Performed prior to administration of the investigational product, ( ) Performed as needed at the discretion of the investigator.
** The laboratory tests performed at the screening will be used to confirm the subject's eligibility for participation.
# The screening visit and Day 1 can be performed on the same day. Administration of vancomycin/investigational product is recommended as soon as possible after randomization.

1 Informed consent: The informed consent explanation and consent process will be completed prior to the start of any procedures associated with the study.

2 Demographic data: The age (year and month of birth) and gender of the subjects will be collected.

3 Medical history and current medical conditions: The medical history within 3 months of the screening visit (or within 5 years for malignancies) will be obtained. The collected medical history will also be checked for its relevance to MRSA bacteremia. For subjects with suspected endocarditis, echocardiography can be performed at the discretion of the investigator. If subjects have results of previous tests at the time of screening, these results will be taken as a medical history.

4 Prior medications: Information about medications administered within 30 days prior to the screening visit will be collected.

5 Vital signs: Systolic/diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured. Measurements will be taken at the time of screening, Day 1, Day 3, Day 5, and Day 7, and then at weekly intervals (Day 14, Day 21, Day 28, Day 35, Day 42), and at the EOT/DC/TOC visit. Additional measurements will be taken as deemed necessary by the investigator.

6 Body measurement: Height will be measured only at the time of screening. If a measurement is available before the screening, the most recent result will be collected. Body weight will be measured at screening and at the EOT/DC visits. If the data are available to two decimal places, they will be rounded to one decimal place for collection.

7 Physical examination: Physical examination will be performed at the time of screening, Day 1, Day 3, Day 5, and Day 7, and then at weekly intervals (Day 14, Day 21, Day 28, Day 35, Day 42), and at the EOT/DC/TOC visit. Additional examinations will be performed as deemed necessary by the investigator.

8 Laboratory tests: For laboratory tests performed at the screening visit, with the exception of pregnancy tests, results obtained within 1 week (7 days) prior to the screening visit may be used. However, for clinically significant abnormal results, the tests should be performed at the screening visit. The laboratory tests will be performed on Day 1 and Day 7 and then weekly (Day 14, Day 21, Day 28, Day 35, Day 42). Additional tests will be taken as deemed necessary by the investigator. At the EOT visit, the test can be omitted if the results of the previous 3 days are available. For women of childbearing potential, serum or urine pregnancy tests will be performed at screening, and participation is allowed if the result is negative. Further pregnancy tests can be performed at the discretion of the investigator.

Laboratory Tests	Test Items	Collection Volume
Hematology	RBC, hemoglobin, hematocrit, platelet, ANC, WBC, WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Blood: About 15 mL per collection Urine: About 15 mL per collection
Blood chemistry	albumin, total protein, alkaline phosphatase, ALT, AST, γ-GT[a),b)], total bilirubin, blood urea nitrogen (BUN), creatinine, uric acid, glucose, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), phosphorus (P), C-reactive protein (CRP), creatine phosphokinase (CPK)[a)], triglyceride [a),b)]	
Coagulation[c)]	PT (INR), aPTT	
Urinalysis	pH, occult blood, glucose, albumin (protein), urine microscopy (RBC, WBC), bacteria	
Pregnancy test	Serum or urine HCG (only for women of childbearing potential)	

a) These tests are not performed at the screening visit.
b) The test are performed on Day 1, Day 14, and at the EOT visit. At the EOT visit, the test can be omitted if the results of the previous 3 days are available.
c) These tests are performed at screening and at the EOT visit.

9 12-lead ECG: The ECG will be performed at screening and at the EOT visit to confirm the presence of clinically significant abnormal results. Additional ECGs can be performed as deemed necessary by the investigator. The results at the time of screening can be substituted if the results are available within 3 days prior to screening. However, if there are clinically significant abnormal results, the ECG will be performed at the screening visit.

10 Blood cultures: Two sets of blood cultures will be collected from different sites if possible and performed consecutively (1 set = 2 bottles; 1 anaerobic and 1 aerobic, approximately 20 mL per set). According to the inclusion criteria, at least one positive MRSA test result is required before randomization. Blood cultures will be performed at screening, on Day 3, Day 5, and Day 7, and then every 3 days until MRSA results are confirmed negative twice consecutively (i.e., if the first negative result is obtained, the second test will be performed within 3 days to confirm the second negative result). The blood cultures will also be performed on Day 14 and at the EOT visit. If the MRSA results are confirmed negative twice consecutively before the EOT visit, no blood cultures will be performed at the EOT visit. Additional blood cultures may be performed as deemed necessary by the investigator. Blood cultures performed for MRSA confirmation at screening can be based on results obtained during routine medical care prior to obtaining consent. However, the test results must be obtained either within 72 hours prior to randomization or within 96 hours prior to randomization if empirical treatment with vancomycin is initiated within 72 hours (compliance with inclusion criterion 2). The identification of MRSA can also be confirmed by rapid test results from each study site.

11 Vancomycin/LCB01-0371 MIC evaluation: Evaluation of the MIC of vancomycin may be performed after the time of screening at the investigator's discretion to confirm susceptibility, determine resistance to MRSA, and adjust the vancomycin dose. In addition, MIC_{BMD} analysis can be performed at a designated laboratory by transferring samples when necessary.
The MIC of LCB01-0371 will be analyzed on Day 14 in subjects whose blood culture results are not negative conversion by Day 14 after screening. In subjects who discontinue treatment before Day 14 or whose blood cultures are not negative conversion by the EOT visit, the MIC of LCB01-0371 will be evaluated at the EOT visit. However, this evaluation will be performed only when possible and at a designated laboratory.

12 Efficacy assessment: Efficacy assessment will be conducted on Day 3, Day 5, Day 7, Day 14, at the EOT visit, and at the TOC visit, which includes evaluation of clinical symptoms and signs of MRSA bacteremia, review of blood culture results, determination of MRSA bacteremia relapse, and occurrence of death. The blood culture results from each assessment time point will be reviewed at the following efficacy assessment.

13 PK assessment: For the pharmacokinetic assessments, a single blood sample will be collected at each blood sampling time point on Day 1 and from Day 3 to the EOT visit.

No.	Day	Blood Sampling Time Point		No.	Day	Blood Sampling Time Point	Collection Volume (mL)
1	1	30min-1h		3	From Day 3 to EOT	30min-1h	8 mL
2		2h-8h		4		2h-8h	8 mL

14 Administration of the investigational product/vancomycin: According to the inclusion criteria, at least one positive MRSA result from a blood culture performed prior to randomization is required for enrollment in the study. Subsequently, subjects will be randomized to either the standard vancomycin treatment group or the vancomycin plus LCB01-0371 combination treatment group and will receive the investigational product from Day 1 to a maximum of 42 days (at least 14 days). If the investigator determines that a switch to an antibiotic other than vancomycin is necessary for the treatment of persistent MRSA bacteremia after at least 7 days of vancomycin administration, a switch to daptomycin is allowed. After at least 14 days of vancomycin therapy (including switching to daptomycin), an oral antibiotic (excluding oxazolidinones) can be administered at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.
The dosage and administration of vancomycin can be adjusted based on the TDM results performed according to institutional guidelines and the judgment of the investigator.

15 Concomitant medication/combination therapy: After the baseline visit, information on concomitant medications administered from the time points indicated in the schedule of activities, including drug names (generic names), purpose of administration, daily dosage, route of administration, and duration of treatment, will be collected and recorded in the CRF.

16 All primary lesions of MRSA infection observed from screening to the end of the study, including whether they are removed, and any bacteremia-related reactions will be collected. Clinical symptoms, laboratory test results, vital signs, and other responses will be recorded under a single diagnosis. Symptoms and signs related to the exacerbation of primary lesions from MRSA infection and bacteremia following the administration of the investigational product will be collected as AEs related to “MRSA bacteremia”. However, if the exacerbation is not due to the underlying MRSA infection or does not correspond to the expected clinical manifestations associated with MRSA bacteremia, it will be collected as an AE or SAE.

17 Any clinically significant medical conditions or abnormalities observed from the administration of the investigational product until the end of the study will be collected as AEs. Clinically significant abnormal findings will also be collected as AEs, and any AEs confirmed before administration of the investigational product will be collected as new AEs if their severity worsens after administration.

18 Subjects who discontinue treatment with the investigational product will undergo the scheduled EOT visit within +2 days of the last administration of the investigational product or the decision to discontinue treatment and will be considered withdrawn. However, subjects who discontinue treatment, with the exception of those who voluntarily withdraw consent, will undergo the TOC visit 28 days (±4 days) after the EOT visit to complete the study.

3 Introduction

3.1 Study Background

Staphylococcus aureus (*S. aureus*) is a widespread pathogen that causes infections in humans. It primarily colonizes the nasopharynx, skin, nasal cavity, and gastrointestinal tract, and is known to cause a variety of infections, including skin and soft tissue infections, pneumonia, osteoarthritis, and bacteremia. It is also reported as a major cause of healthcare-associated infections. The increasing use of catheters, prostheses, and invasive procedures has led to an increase in serious infections caused by S. aureus. Many of these strains are resistant to existing antibiotics, making effective antibiotic treatment more challenging.[1,2] Since the emergence of methicillin-resistant *S. aureus* (MRSA) in 1961, resistance to antibiotics has developed rapidly, leading to an increase in the frequency of MRSA infections. MRSA is a major causative pathogen of hospital-acquired infections, and recently, community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) has emerged as a new problem not only in hospitals but also in the community. Although a direct comparison of antibiotic resistance rates is difficult due to the lack of standardized testing methods and surveillance systems between countries, the methicillin resistance rate of S. aureus in Korea is 67.7%, which is significantly higher than in the UK (13.6%), France (20.1%), and Japan (53%).[3]

In addition, the continuous increase in vancomycin use in MRSA infections led to the reporting of vancomycin-intermediate *S. aureus* (VISA) in 1996, and vancomycin-resistant *S. aureus* (VRSA) has been reported since 2002, making antibiotic resistance in *S. aureus* a very serious problem.[4,5]

MRSA bacteremia is a serious infection of the bloodstream and is associated with a high mortality rate among the various infectious diseases.[6] The mortality rate for MRSA bacteremia is approximately 20-40%, and it is known to be more difficult to treat and more fatal than S. aureus bacteremia.[5] Therefore, timely treatment with appropriate antibiotics plays a crucial role in improving patient survival.

According to the Infectious Diseases Society of America (IDSA) guidelines, intravenous injection of vancomycin or daptomycin for at least 2 weeks and up to 6 weeks is recommended as first-line therapy for MRSA bacteremia. If treatment with vancomycin fails, high-dose daptomycin (10 mg/kg/day) is preferred, although combination therapies with gentamicin, rifampin, linezolid, or beta-lactam antibiotics are also recommended.[8]

Vancomycin is a glycopeptide antibiotic that has a bactericidal effect by inhibiting bacterial cell wall synthesis and is currently the preferred antibiotic for the treatment of MRSA bacteremia. However, vancomycin has a slower bactericidal effect than oxacillin, has poor penetration into pulmonary tissue and the central nervous system, and is associated with increasing minimum inhibitory concentrations (MICs) for MRSA (a phenomenon known as "MIC creep"), which limits its efficacy in the treatment of MRSA bacteremia.[8,9] For vancomycin, maintaining an area under the curve (AUC)/MIC ratio of at least 400 is critical for optimal therapeutic efficacy. If the MIC of the causative organism increases, the AUC must also increase accordingly. Newer MRSA isolates often have MICs of 1 or 2 μg/mL, making it difficult to maintain an AUC/MIC ratio of 400 or higher, which has led to an increase in vancomycin treatment failure rates. In the treatment of bacteremia associated with severe infections such as infective endocarditis, osteomyelitis, and pneumonia, higher doses of vancomycin are required, which increases the risk of nephrotoxicity.[10] In addition, the increased use of vancomycin has led to an increase in resistant strains such as heterogeneous vancomycin-intermediate *S. aureus* (hVISA), highlighting the need for new antibiotics and combination therapies to effectively treat multidrug-resistant *S. aureus* infections.[10-12]

Recently, several new antibiotics that are effective against MRSA, such as daptomycin, linezolid, and ceftaroline, have been developed and are now being used in clinical practice. Daptomycin, a cyclic lipopeptide antibiotic, is being considered as an alternative to vancomycin. However, its poor penetration into pulmonary tissue makes it unsuitable for the treatment of respiratory tract infections, and rhabdomyolysis has been reported as a side effect.[6,8] In addition, despite the non-inferiority of newly developed drugs to vancomycin in the treatment of MRSA bacteremia, none of them has shown clear superiority. Due to their high cost and significant side effects, vancomycin continues to be used as the first-line choice against MRSA bacteremia.[9,11,14] When treatment with vancomycin fails, new antibiotics such as daptomycin and linezolid, either alone or in combination, are being considered as treatment alternatives.

Antibiotic combination therapy aims to reduce the development of resistance and improve the antimicrobial effect through different mechanisms of action. However, alternatives to vancomycin, such as daptomycin, β-lactam antibiotics, and linezolid, have not shown improved antimicrobial activity in combination with vancomycin.[10,15,16] The mechanism of action of vancomycin is bactericidal by inhibiting bacterial cell wall synthesis by attaching to the bacterial cell wall and blocking glycopeptide polymerization. LCB01-0371, developed by LegoChem

Biosciences, Inc. for the treatment of MRSA bacteremia, is an oral oxazolidinone antibiotic. It binds to domain V of bacterial 23S ribosomal ribonucleic acid (rRNA), inhibiting the formation of the initial complex between 30S and 50S rRNA, thereby suppressing bacterial protein synthesis and providing antimicrobial activity.[17] Furthermore, due to its different mechanism of action compared to vancomycin, it has no cross-resistance, which facilitates combination therapy and could reduce the risk of resistance development to enhance the antibacterial effect.

3.2 Study Rationale

Oxazolidinone antibiotics have a novel mechanism of action in which they inhibit bacterial protein biosynthesis by binding to the V domain of 23S rRNA in the bacterial 50S ribosome subunit, thereby interfering with the initial complex formation of 30S rRNA and 50S rRNA. This different mechanism of action provides the advantage that there is no cross-resistance with existing antibiotics.[17] Linezolid, a representative oxazolidinone antibiotic, is effective against Gram-positive bacteria and shows excellent antimicrobial activity against skin and soft tissue infections, pneumonia, and multidrug-resistant Gram-positive bacteria such as MRSA, VRSA, and VRE.[1]With the increased clinical use of linezolid, resistant strains of *S. aureus* and *enterococci* have been increasingly reported in the United States and Europe. Moreover, long-term use of linezolid is severely limited due to its bone marrow toxicity, including inhibition of monoamine oxidase, thrombocytopenia, anemia, and neutropenia.[6,18,19] Therefore, there is a need to develop new oxazolidinone antibiotics that can overcome resistance to linezolid and improve its toxicity profile.

LCB01-0371, developed by LegoChem Biosciences, Inc., is an oral tablet oxazolidinone antibiotic that has fewer bone marrow toxicity compared to linezolid and shows superior antimicrobial activity against most Gram-positive bacteria and multidrug-resistant Gram-positive bacteria compared to linezolid. In a bacteremia mouse model, combination therapy of LCB01-0371 and vancomycin showed a greater reduction in viable blood cell counts than vancomycin monotherapy, suggesting potential synergistic antimicrobial effects through the combination of vancomycin and LCB01-0371.

Therefore, this phase 2 clinical study aims to investigate the efficacy, safety, and pharmacokinetic properties of LCB01-0371 in combination with vancomycin compared to standard vancomycin therapy in patients with MRSA bacteremia.

3.3 Benefit and Risk Assessment

3.3.1 Nonclinical Experience

The key nonclinical results are as follows, and detailed information can be found in the investigator's brochure.[17]

1) Efficacy Study

① Mouse systemic infection model (Study LCB01-0371-PH-04)

In the systemic infection model in mice induced by various Gram-positive and Gram-negative bacteria, including *S. aureus* Giorgio and *H. influenzae hd2*, comparison of antimicrobial activity between LCB01-0371 and linezolid showed that LCB01-0371 demonstrated stronger antimicrobial activity with a lower ED_{50} value than linezolid.

② *In vitro* MIC test and *in vivo* efficacy study in a bacteremia infection mouse model using the *S. aureus* Giorgio

- In vitro MIC test: In the *S. aureus* Giorgio strain, the MIC values for LCB01-0371, linezolid, and vancomycin were found to be 1 mg/L, 1 mg/L, and 0.5 mg/L, respectively. LCB01-0371 showed similar antimicrobial activity to linezolid and vancomycin.
- Confirmation of the effect of LCB01-0371 and vancomycin in the blood of the bacteremia mouse model: To establish the bacteremia mouse model, a bacterial suspension of *S. aureus* Giorgio was administered at a concentration of 5 x 10^6 CFU/mouse. One hour after infection, LCB01-0371 and vancomycin were administered subcutaneously (S.C.), while the control group received no treatment. In the control group, the number of viable cells increased over time, with all animals dying after 24 hours. In the LCB01-0371 80 mg/kg group, the number of viable cells decreased similarly to the vancomycin 40 mg/kg group, with the number of viable cells in both groups being significantly lower from 12 hours than at 1 hour post-infection. These results indicate that LCB01-0371 80 mg/kg demonstrates similar antimicrobial activity to vancomycin 40 mg/kg against *S. aureus* Giorgio.

- Confirmation of the effect of LCB01-0371 and linezolid in the blood of the bacteremia mouse model: In the mouse systemic infection model induced by a bacterial suspension of *S. aureus* Giorgio, evaluation of the effects of LCB01-0371 and linezolid on the number of viable blood cells showed that the control group had increased viable cell counts and death of all animals at 24 hours, while the LCB01-0371 25, 50, and 100 mg/kg groups showed decreased viable cell counts. From 12 hours onwards, all three groups showed significantly lower numbers of viable cells than at 1 hour post-infection with *S. aureus* Giorgio, with the LCB01-0371 50 and 100 mg/kg groups showing similar levels to the linezolid 50 mg/kg group.
- Evaluation of the effects of LCB01-0371, vancomycin, and linezolid in the blood and spleen of the bacteremia mouse model: The effects of LCB01-0371, vancomycin, and linezolid on the number of viable cells in the blood and spleen tissue were investigated in a mouse systemic infection model induced by a bacterial suspension of *S. aureus* Giorgio. The control group showed an increased number of viable *S. aureus* Giorgio cells in the blood and spleen tissue, and all animals died after 24 hours. On the other hand, the LCB01-0371 50 and 200 mg/kg, vancomycin 25 mg/kg, and linezolid 50 mg/kg treatment groups showed a decreased number of viable cells in the blood up to 24 hours post-infection, which was significantly lower than the number 1 hour post-infection. In the spleen, no significant dose dependent differences in the number of viable cells were observed between the LCB01-0371 50 and 200 mg/kg groups.
- Confirmation of the combination effect of LCB01-0371 and vancomycin in the blood and lung of the bacteremia mouse model: In the mouse systemic infection model induced by a bacterial suspension of *S. aureus* Giorgio, the effects of LCB01-0371 administration methods (S.C. or P.O.) and the combination with vancomycin on the number of viable cells in the blood and lung tissue were evaluated. The control group showed an increased number of viable *S. aureus* Giorgio cells in the blood and lung tissue and all animals died after 24 hours. On the other hand, the LCB01-0371 50 mg/kg S.C. or P.O. group, the vancomycin 25 mg/kg S.C. group, the group with the combination of LCB01-0371 and vancomycin, and the linezolid 50 mg/kg group showed a reduced number of viable cells in the blood and lung tissue up to 24 hours post-infection, which was significantly lower than the number of cells at 1 hour after infection. There were no significant differences in the number of viable *S. aureus* Giorgio cells in the blood and lung tissue depending on the type of drug or the method of administration. However, the LCB01-0371 and vancomycin combination group had a lower number of viable cells in the blood after 24 hours than the LCB01-0371 or vancomycin monotherapy group.

2) Safety Pharmacology

To evaluate the cardiovascular safety of LCB01-0371, a human ether-à-go-go related gene (hERG) assay was performed with the HEK293 cell line. As a result, LCB01-0371 showed no significant effect on inward rectifying potassium current at concentrations of 0.1 - 100 μM (Study 1756-005).

Single oral administration of LCB01-0371 at doses of 250, 500, and 1000 mg/kg in mice resulted in no deaths, clinical signs (changes in physical condition, activity/arousal, autonomic nervous system or changes in neurobehavioral assessment of neuromuscular or sensorimotor function), or effects on respiratory rate (breaths per minute) or tidal/minute volume (Study 1756-006, 1756-007).

In beagle dogs, single oral administration of LCB01-0371 at doses of 120, 300, and 750 mg/kg or single intravenous administration (IV infusion) at doses of 50, 150, and 300 mg/kg over 1 hour showed no adverse events in clinical observations, body temperature, blood pressure, heart rate, and ECG examinations (Study 1756-008, 1756-017).

3) PK Assessment

LCB01-0371 was administered orally to mice, rats, and dogs to evaluate its absorption, distribution, metabolism, and excretion (ADME).

① Absorption and bioavailability

Absorption and bioavailability: Bioavailability was 60-70% in mice and dogs, and 100% in humans. No accumulation of LCB01-0371 was observed after 28 days of repeated administration in mice and dogs and after 21 days of repeated administration in humans.

- Oral administration

When LCB01-0371 was administered orally to male CD-1 mice at a dose of 30 mg/kg, the mean maximum serum concentration (C_{max}) was 24.45 mg/L, the mean time to maximum plasma concentration (T_{max}) was 0.5 hr, the mean half-life ($T_{1/2}$) was 1.11 hr, and the area under the plasma concentration-time curve from zero to infinity

($AUC_{0-\infty}$) was 48.28 mg·hr/L (Study LCB01-0371-PK-01).

When LCB01-0371 was administered orally to male Sprague-Dawley rats at a dose of 10 mg/kg (Study LCB01-0371-PK-02), the mean C_{max} was 4.03 mg/L, the mean T_{max} was 1.17 hr, the mean $T_{1/2}$ was 1.13 hr, the mean $AUC_{0-\infty}$ was 16.24 mg·hr/L, and the apparent bioavailability was 68.6% (Study LCB01-0371-PK-02).

When LCB01-0371 was administered orally to male beagle dogs at a dose of 10 mg/kg, the mean C_{max} was 11321.97 ng/mL, the mean T_{max} was 0.67 hr, the mean $T_{1/2}$ was 3.27 hr, the mean $AUC_{0-\infty}$ was 48.745 mg·hr/mL, and the apparent bioavailability was 58.54%. When LCB01-0371 was administered orally to male beagle dogs at a dose of 30 mg/kg, the mean C_{max} was 28751.20 ng/mL, the mean T_{max} was 0.33 hr, the mean $T_{1/2}$ was 3.43 hr, the mean $AUC_{0-\infty}$ was 151.345 mg·hr/mL, and the apparent bioavailability was 60.59% (Study LCB-0901).

In repeated-dose toxicokinetic studies of LCB01-0371 in Sprague-Dawley rats and beagle dogs, no differences in PK parameter values were observed between males and females. Exposure to LCB01-0371 increased dose-proportionally, and no drug accumulation was observed except in rats receiving 400 mg/kg/day.

② Distribution

In the plasma protein binding study, LCB01-0371 showed protein binding rates of 69% in mice, rats, and dogs, and 37% in humans (Study LCB01-0371-ADME-04). The stability of LCB01-0371 in the plasma of mice, rats, dogs, and humans was confirmed for 2 hours (Study LCB01-0371-ADME-05).

In the mass balance study in Sprague-Dawley rats, LCB01-0371 was distributed from tissues associated with the gastrointestinal tract (esophagus, stomach, small intestine, etc.) to tissues not associated with the gastrointestinal tract (lungs, heart, skin, etc.) within 2 hours of oral administration and then gradually decreased and was detected only in the intestinal contents, adrenal glands, and liver at 48 hours after administration (Study 1756-016).

③ Metabolism

The half-life of LCB01-0371 in the liver microsomes of rats, dogs, and humans were more than 60 minutes (Study LCB01-0371-ADME-01), and a total of 17 metabolites were identified in rat, dog, and human plasma (Study I17-001).

The investigation of the potential of LCB01-0371 to induce and inhibit cytochrome P450 (CYP) isoenzymes showed that LCB01-0371 did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 isoenzymes (Study B32-160004-03, Study B32-160004-04). In addition, investigation of the effects of LCB01-0371 on drug transporters showed that it did not inhibit the transport activity of OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, or NTCP (Study B32-160004-01, Study B32-160004-02).

④ Excretion

In the mass balance study with male Sprague-Dawley rats, the primary route of excretion was urine, followed by fecal excretion. Specifically, at 168 hours after administration, the mean cumulative urinary recovery was 66% (97% of which was excreted within 24 hours), and the mean cumulative fecal recovery was 24% (93% of which was excreted within 48 hours) (Study 1756-016).

4) Toxicology

Toxicity was evaluated in Sprague-Dawley rats and beagle dogs after single and repeated oral and intravenous administration of various concentrations of LCB01-037. Repeated dose studies included recovery periods of 4, 26, and 39 weeks, respectively. Single and repeated-dose toxicity studies showed no serious adverse events or direct target organ toxicity, and the overall results were comparable to those reported for other oxazolidinone antibiotics.

- **Single dose**

Sprague-Dawley rats (Study No. 1756-009, 020): After single oral administration of LCB01-0371 at doses of 0, 250, 500, 1,000, 2,000 mg/kg/day and single intravenous administration at doses of 0, 250, 500, 1,000, 1,800 mg/kg/day, the maximum tolerated dose (MTD) in rats was determined to be 2,000 mg/kg and 1,000 mg/kg/day, respectively.

Beagle dogs (Study No. 1756-010, 021): After single oral and intravenous administration of LCB01-0371 at doses of 0, 125, 250, 500, and 1,000 mg/kg, the MTD in beagle dogs was determined to be 1,000 mg/kg/day and 500 mg/kg/day, respectively.

- **Repeat dose**

① 28-Day oral toxicity study in rats (Study No. 1756-011)

After twice-daily oral administration of LCB01-0371 at doses of 0, 30, 60, 140 mg/kg/day to Sprague-Dawley rats for 28 days, the no observed adverse effect level (NOAEL) was 60 mg/kg/day, with corresponding C_{max} and AUC_{0-24} on Day 28 of 11.2 mg/L and 50.4 mg·hr/L, respectively. Some rats receiving 140 mg/kg/day showed clinical and histological abnormalities, which disappeared during the recovery period.

② 26-Week oral toxicity study in rats (Study No. B15186)

After twice-daily oral administration of LCB01-0371 at doses of 0, 10, 25, 50, or 100→75 mg/kg/day to Sprague-Dawley rats for 26 weeks, the NOAEL in males was 10 mg/kg/day, with corresponding C_{max} and AUC_{0-24} on Day 182 of 2.9 mg/L and 10.1 mg·hr/L, respectively. In females, the NOAEL was 100→75 mg/kg/day, with corresponding C_{max} and AUC_{0-24} on Day 182 of 14.8 mg/L and 58.0 mg·hr/L, respectively. Some rats receiving 50 or 100→75 mg/kg/day showed hematological and histological abnormalities, and these hematological abnormalities and some histological abnormalities recovering during the recovery period.

③ 28-Day oral toxicity study in beagle dogs (Study No. 1756-012)

After twice-daily oral administration of LCB01-0371 at doses of 0, 5, 10, or 20 mg/kg/day to beagle dogs for 28 days, the NOAEL in males was 20 mg/kg/day, with corresponding C_{max} and AUC_{0-24} on Day 27 of 11.2 mg/L and 54.9 mg·hr/L, respectively. In females, the NOAEL was 10 mg/kg/day, with corresponding C_{max} and AUC_{0-24} on Day 27 of 6.1 mg/L and 35.4 mg·hr/L, respectively.

④ 39-Week oral toxicity study in beagle dogs (Study No. B15189)

After twice-daily oral administration of LCB01-0371 at doses of 0, 2, 5, 10, or 20→15 mg/kg/day to beagle dogs for 39 weeks, the NOAEL was 10 mg/kg/day for both males and females. No deaths occurred in either sex, and no test substance-related toxic effects were observed in the ophthalmologic examination, ECG, urinalysis, organ weights, and necropsy.

- **Genotoxicity**

To evaluate the genotoxicity of LCB01-0371, a bacterial reverse mutation assay, mouse lymphoma mutagenesis assay using L5178Y/TK+/- cells, rat micronucleus assay, and chromosome aberration assay using human peripheral blood lymphocytes were performed. Various in vitro and in vivo genotoxicity tests showed that LCB01-0371 was negative for mutagenicity and micronucleus formation and had no structural chromosome aberration potential.

- **Reproductive Toxicity**

Studies on fertility, early embryonic development toxicity up to implantation, and embryo-fetal development toxicity were conducted in rats.

① Reproductive toxicity study in rats (Study B15192)

LCB01-0371 was administered orally to male Sprague Dawley rats from 4 weeks before mating until necropsy and to female rats from 2 weeks before mating until implantation at doses of 15, 30, and 60 mg/kg/day to evaluate reproductive and developmental toxicity. Male rats receiving 30 and 60 mg/kg/day showed a dose-dependent decrease in sperm motility and an increase in abnormal sperm. Histopathological examination revealed retention of sperm cells in the testis, oligospermia, and intraluminal cell debris in the epididymis in one male rat at 15 mg/kg/day and in several male rats at 30 and 60 mg/kg/day. Based on these results, the lowest observed adverse effect level (LOAEL) for male rats was determined to be 15 mg/kg/day, and the NOAEL for female rats was 60 mg/kg/day.

② Reproductive and developmental toxicity study in rats (Study B15194)

After oral administration of LCB01-0371 at doses of 15, 30, and 60 mg/kg/day to female Sprague Dawley rats from gestation day 7 to 17, fetuses from females receiving 60 mg/kg showed decreased body weights, and rats receiving 30 and 60 mg/kg showed decreased placental weights. Fetuses from females receiving 60 mg/kg showed visceral variations, including increased cervical thymic remnants and decreased ureteral ridge and dilatation, and skeletal variations, including a lack of ossification of the 5th and 6th sternebrae and significantly decreased ossification of the sternum, sacrococcygeal vertebrae, forelimbs, and hindlimbs. No abnormalities were noted on external examination of the fetus and observation of the placenta. The maternal NOAEL was confirmed as 30

mg/kg/day, and the NOAEL for embryonic development was determined to be 15 mg/kg/day based on fetal weight, placental weight, visceral and skeletal variations, and number of ossifications.

③ Embryo-fetal toxicity study in rabbits (Study B15195)

After oral administration of LCB01-0371 at doses of 0, 1, 3, and 10 mg/kg/day to female New Zealand White rabbits during organogenesis (gestation days 6-18), no differences in fetal weight, placental weight, external examination of the fetus, or observation of the placenta were observed in all dose groups compared to the control group. Visceral and skeletal observations of the delivered fetuses also showed no differences compared to the control group. However, maternal animals receiving 10 mg/kg/day showed LCB01-0371-related effects, including premature birth, abortion, delivery status, decreased body weight, and decreased food consumption. Based on these results, a high and low dose of 3 and 0.3 mg/kg/day, respectively, was established.

3.3.2 Clinical Experience

A total of six Phase 1 studies (5 with oral formulation, 1 with intravenous formulation) were conducted in healthy adult male volunteers and one Phase 2a study (with oral formulation) in tuberculosis patients.

- **Safety Assessment Results**

A total of 239 subjects received the investigational product LCB01-0371 for up to 21 days. Based on previous study results of LCB01-0371, the safety data collected from 239 subjects showed a similar safety profile to other oxazolidinone antibiotics, and the MTD for repeated administration over 21 days was confirmed to be 2,400 mg per day.

The most frequent adverse events reported in previous clinical studies were headache, nausea, dizziness, decreased neutrophil count, diarrhea, abdominal discomfort, increased total bilirubin, rhinorrhea, dyspepsia, vomiting, myalgia, decreased appetite, and asthenia, with no significant signs of bone marrow suppression observed.

- **PK Assessment Results**

After a single oral administration of LCB01-0371, the PK parameters showed dose proportionality in the dose range of 50-3,200 mg. Compared to linezolid ($T_{1/2}$: 7.94 hr), the $T_{1/2}$ of LCB01-0371 was 1.41-3.41 hr, and therefore, BID dosing of LCB01-0371 was considered appropriate.

The mean absolute bioavailability of LCB01-0371 was 99.75% at the AUC after oral administration. Although the C_{max} equivalence was insufficient, this was considered clinically insignificant as the efficacy of LCB01-0371, like that of other oxazolidinones, correlates best with the AUC/MIC ratio and not with peak exposure (C_{max}).

In repeated-dose studies, the PK parameters of LCB01-0371 were similarly observed after 7 or 21 days of administration, suggesting that long-term administration of LCB01-0371 does not significantly affect the ADME of the drug. Negligible accumulation of the drug, rapid clearance, and large inter-individual variability were observed after 21 days of administration.

When LCB01-0371 was administered with a high-fat diet, absorption was delayed, the maximum blood concentration decreased, and the AUC decreased by 10% compared to administration under fasting conditions. However, since the delay in absorption (T_{lag}) of LCB01-0371 after a high-fat diet was 21 minutes, the food effect was considered insignificant.

A summary of individual results from previous studies can be found in Table 1. Detailed information can be found in the investigator's brochure.[17]

Table 1. Summary of Previous Study Results

Study No.	Phase/Objective(s)/Study Design	Dosage and Administration	Target Population	Study Results
LCB01-0371-11-1-01	Phase 1a To evaluate safety, tolerability, PK, and PD Double-blind, randomized, placebo-controlled, single ascending dose	Single dose LCB01-0371: 50, 100, 200, 400, 800, 1,600, 2,400, 3,200 mg Placebo Linezolid 600 mg	Healthy male volunteers 6 subjects per treatment group 15 subjects 6 subjects	1. The most commonly reported adverse events included a decrease in neutrophil count (5 subjects), an increase in total bilirubin (4 subjects), nausea (3 subjects), headache (2 subjects), and vomiting (2 subjects). 2. Clinically significant abnormal laboratory test results were observed in 12 subjects and reported as adverse events, including a decrease in neutrophil count, an increase in total bilirubin, an increase in creatine kinase, and hypertriglyceridemia. No significant changes were observed in vital signs and ECG examinations. 3. The severity of adverse events that occurred up to the dose escalation to 2,400 mg was mostly mild, with moderate adverse events reported only in the 3,200 mg group. In the 3,200 mg group, gastrointestinal adverse events were reported, which were considered attributable to taking sixteen 200 mg tablets. Therefore, the MTD in the single-dose study is determined to be 2,400 mg per day. 4. The blood concentration increased in proportion to the dose increase. The half-life was 1.41-3.41 hours, which was shorter than that of linezolid (7.94 hours). Considering the half-life, BID regimen is considered appropriate.
LCB01-0371-12-1-02	Phase 1b To evaluate safety, tolerability, PK, and PD Double-blind, randomized, placebo-controlled, multiple ascending dose	Part 1: 7-Day repeat dose LCB01-0371: 400, 800, 1,200, 1,600 mg BID Placebo Part 2: Single dose LCB01-0371 800 mg	Healthy male volunteers 6 subjects per treatment group 8 subjects 6 subjects	1. The most commonly reported adverse events were headache (6 subjects), nausea (5 subjects), dizziness (4 subjects), and abdominal discomfort (3 subjects). 2. Laboratory test results revealed clinically significant abnormal changes reported as adverse events in 5 subjects, including a decrease in neutrophil count, hypertriglyceridemia, an increase in urine WBC, an increase in creatine kinase, and an increase in AST. No significant changes were observed in vital signs and ECG examinations. 3. The severity of adverse events was mostly mild, with moderate adverse events leading to permanent discontinuation of treatment reported only in the 1,600 mg group. 4. Tolerability was confirmed by dose escalation up to 1,200 mg BID with repeated dosing over 7 days, and no safety-related adverse events were reported. Therefore, the MTD in the 7-day repeated dose study is determined to be 1,200 mg BID (2,400 mg per day). 5. The blood concentration increased in proportion to the dose increase.
LCB01-0371-14-1-01	Phase 1b Safety, tolerability, popPK Double-blind, randomized, placebo-controlled, multiple ascending dose	21-Day repeat dose LCB01-0371 800 mg QD LCB01-0371 800 mg BID LCB01-0371 1,200 mg BID Placebo	Healthy male volunteers 13 subjects 10 subjects 10 subjects 6 subjects	1. The most commonly reported adverse events were diarrhea (6 subjects), rhinorrhea (4 subjects), dizziness (3 subjects), dyspepsia (3 subjects), headache (3 subjects), nausea (3 subjects), abdominal discomfort (2 subjects), asthenia (2 subjects), and a decrease in neutrophil count (2 subjects). 2. The severity of adverse events was mostly mild, with the exception of the decrease in neutrophil count and abnormal changes in hematology and liver

Study No.	Phase/Objective(s)/Study Design	Dosage and Administration	Target Population	Study Results
				function tests. 3. In the LCB01-0371 treatment group, 1 subject experienced adverse events leading to treatment discontinuation (1 subject with abnormal changes in hematology and liver function tests), and 2 subjects experienced adverse events leading to treatment interruption (decrease in neutrophil count in 1 subject; headache, cold symptoms, and diarrhea in 1 subject). In addition, 2 subjects in the LCB01-0371 treatment group permanently discontinued treatment due to abnormal laboratory test results (ANC decrease, aPTT increase), although these were not reported as adverse events. No clinically significant changes were observed in vital signs and ECG examinations. 4. There were no serious adverse events such as bone marrow toxicity (e.g., bone marrow suppression), which was reported during the 21-day repeated administration of linezolid at a dose of 800 mg BID or 1,200 mg BID, and other serious adverse events. Therefore, the MTD is determined to be 1,200 mg BID (2,400 mg per day). 5. The results of the PK analysis after 21 days of repeated administration were confirmed to be similar to the results of the PK analysis after 7 days of repeated administration. Therefore, long-term administration is not expected to have a significant effect on the ADME of LCB01-0371.
LCB01-0371-13-1-03	Phase 1c To evaluate food effect on PK and bioequivalence and compare two tablet formulations (bilayer extended-release tablet vs. currently developed tablet formulation) Randomized, open-label, single dose, crossover study	Single dose LCB01-0371-B 800 mg LCB01-0371 800 mg	Healthy male volunteers 11 subjects 18 subjects	1. In the LCB01-0371 treatment group, 2 subjects experienced adverse events including rhinorrhea, sore throat, cough, pyrexia, non-cardiac chest pain, and headache, and 1 subject in the LCB01-0371-B treatment group experienced dizziness. The severity of all adverse events was reported as mild. 2. No clinically significant changes were observed in laboratory tests, vital signs, and ECG examinations. 3. When LCB01-0371 800 mg was administered after a high-fat diet, absorption was delayed compared to administration under fasting conditions, with a decrease in C_{max} by approximately 20% and AUC by 10%. After administration following a high-fat diet, the median T_{max} was delayed by 1.25 hours, and $T_{1/2}$ was similar. 4. The results of the PK analysis of LCB01-0371-B 800 mg (bilayer extended-release tablet) were generally comparable to those of LCB01-0371 800 mg. 5. The T_{lag} after administration after a high-fat diet was 4.2 minutes and 21 minutes for LCB01-0371-B 800mg and LCB01-0371 800mg, respectively, with no significant differences between administration in the fasted and fed states.
LCB01-0371-15-1-01	Phase 1c To compare bioavailability Non-randomized, open-label, single dose, parallel design	Single dose LCB01-0371-B 400 mg LCB01-0371-B 800 mg LCB01-0371-B 1,200 mg LCB01-0371 400 mg	Healthy male volunteers 6 subjects 0 subjects 0 subjects 0 subjects	1. Early termination was decided due to the need to improve the formulation. 2. Hyperbilirubinemia occurred in 1 subject but was determined to have no causal relationship with the study drug.

Study No.	Phase/Objective(s)/Study Design	Dosage and Administration	Target Population	Study Results
		LCB01-0371 800 mg LCB01-0371 1,200 mg	0 subjects 0 subjects	
LCB01-0371-16-1-01	Phase 1 To compare formulation (IV injection vs. oral tablet), single-blind, To evaluate PK (C_{max}), safety, and tolerability Randomized, placebo-controlled, single dose, Bioavailability study	Single dose LCB01-0371: IV 200 mg* vs placebo IV 400 mg* vs 800 mg tablet IV 800 mg* vs placebo IV 800 mg† vs placebo IV 1,200 mg† vs placebo * 60 min (± 5 min) constant rate infusion † 30 min (± 5 min) constant rate infusion	Healthy male volunteers 6+2 subjects 4+4 subjects 6+2 subjects 6+2 subjects 4+0 subjects	1. Adverse events related to the injection site occurred most frequently and increased in frequency with dose escalation (especially when increasing from 800 mg to 1,200 mg). 2. The injection site adverse events were paresthesia in 3 subjects, pain at the injection site and in the periphery in 2 subjects, and phlebitis in 1 subject. Adverse events that did not occur at the injection site were nausea in 2 subjects, acne in 1 subject, forearm contusion in 1 subject, erythema at the vascular injection site in 2 subjects, skin rash in 1 subject, left chest pain in 1 subject, and sweating in 1 subject. 3. Eight cases of adverse drug reactions were reported (3 cases of injection site dysesthesia, 2 cases of nausea, 1 case of injection site pain, 1 case of peripheral pain, 1 case of sweating). 4. Mild adverse events occurred in the 200 mg to 800 mg groups, and 2 cases of moderate adverse events (Grade 2 nausea in 2 subjects) occurred in the 1,200 mg group, leading to withdrawal of 2 subjects. 5. Most adverse events recovered during the follow-up period without specific treatment, and no deaths or serious adverse events occurred. 6. No clinically significant changes in laboratory tests, vital signs, physical examination, and ECG examination were observed after administration of the investigational product.
LCB01-0371-15-2-01	Phase 2a Early bactericidal activity (EBA), dose, PK Open-label, randomized, active-controlled	14-Day administration LCB01-0371 400 mg BID LCB01-0371 800 mg QD LCB01-0371 800 mg BID LCB01-0371 1,200 mg QD HRZE[a] 3 ~ 5 tablets (adjusted according to body weight) Linezolid 600 mg BID	TB patients 16 subjects 15 subjects 16 subjects 16 subjects 8 subjects 8 subjects	1. The most frequent adverse events were gastrointestinal disorders (nausea, diarrhea, vomiting, etc.). 2. The incidence of adverse events in the LCB01-0371 treatment groups was 27% (4/15 subjects, 12 cases) in the 800 mg QD group, 75% (12/16 subjects, 23 cases) in the 400 mg BID group, 44% (7/16 subjects, 13 cases) in the 800 mg BID group, and 63% (10/16 subjects, 22 cases) in the 1,200 mg QD group, while the incidence in the control groups was 88% (7/8 subjects, 19 cases) in the HRZE group and 63% (5/8 subjects, 16 cases) in the linezolid 600 mg BID group. 3. The incidence of adverse drug reactions in the LCB01-0371 treatment groups was 19% (12/63 subjects, 27 cases), and 50% of subjects in each control group reported adverse drug reactions. 4. Most adverse events and adverse drug reactions were reported as mild. Only 1 subject in the HRZE treatment group reported Grade 3 or higher adverse drug reactions (increase in alanine aminotransferase, increase in aspartate aminotransferase). There were no Grade 4 or higher adverse drug reactions. 5. Three serious adverse events occurred: 1 case of tuberculosis (exacerbation of underlying disease, resulting in death) in the LCB01-0371 400 mg BID group, 1 case of pleural effusion in the HRZE group, and hyperkalemia in 1 subject

Study No.	Phase/Objective(s)/Study Design	Dosage and Administration	Target Population	Study Results
				in the linezolid 600 mg BID group. 6. Four adverse events leading to permanent discontinuation occurred: Tuberculosis (reported term: tuberculosis aggravated) in the LCB01-0371 400 mg BID and 1,200 mg QD groups was assessed as "not related" or "unlikely" to the investigational product, while the increase in alanine aminotransferase and aspartate aminotransferase reported in the HRZE group were assessed as adverse drug reactions for which a causal relationship with the investigational product cannot be excluded. 7. All clinically significant changes in laboratory test results from baseline were considered not related or unlikely related to the investigational product. 8. Although statistically significant changes from baseline were observed in vital signs, physical examination, ECG, peripheral nerve scale, and eye examination results in some subjects, most changes were within the normal range and recovered to normal.

a. HRZE: isoniazid 75 mg, rifampin 150 mg, pyrazinamide 400 mg, ethambutol 275 mg.
TB: tuberculosis

3.4 Justification for Dosage and Administration

The results of the Phase 1b study (LCB01-0371-14-1-01), in which healthy adult males received LCB01-0371 at a dose of 800 mg and 1,200 mg BID for 21 days, showed a maximum tolerated dose (MTD) of 2,400 mg. Common adverse events (AEs) reported following administration of LCB01-0371 included diarrhea, rhinorrhea, dizziness, dyspepsia, headache, nausea, abdominal discomfort, asthenia, and neutropenia. Most AEs were mild and not clinically significant.

Based on the results of the previous Phase 1 study in healthy volunteers, a dose of 1,600 mg (800 mg BID), one level below the maximum tolerated dose, was chosen as the initial dose for this study.

4 Study Objectives

The purpose of this study is to evaluate the efficacy of the combination therapy of LCB01-0371 and vancomycin compared to standard vancomycin therapy in subjects with MRSA bacteremia and to investigate its safety and pharmacokinetic profile.

4.1 Primary Objective

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

4.2 Secondary Objectives

1) Proportion (%) of subjects with overall cure by the 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 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)
7) Safety of the combination therapy with vancomycin and LCB01-0371
8) PK profile of the combination therapy with vancomycin and LCB01-0371

5 Study Population

5.1 Number of Subjects

Total of 100 subjects (50 subjects per group, two groups)

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1) Male or female subjects ≥19 years of age at the time of written consent
2) Subjects in whom at least one set of blood cultures tested positive for MRSA within 72 hours prior to randomization; or subjects in whom at least one set of blood cultures tested positive for MRSA within 96 hours prior to randomization and who started treatment with vancomycin at least 72 hours prior to randomization
3) Subjects who have clinical symptoms or signs of MRSA bacteremia according to the judgment of the investigator
4) Subjects who have voluntarily decided to participate in this clinical study after being fully informed and who have agreed in writing to comply with the study requirements

5.2.2 Exclusion Criteria

Concurrent diseases and medical history

1) Subjects with polymicrobial bacteremia, including Gram-negative bacteria, or infections
2) Subjects who have received treatment within the last 3 months (however, subjects may be enrolled if they have reinfection as determined by the investigator, regardless of prior treatment within 3 months)
3) Subjects who had received empirical antibiotics for more than 96 hours prior to randomization (limited to 72 hours for MRSA-active antibiotics such as vancomycin)
4) Subjects with septic shock
5) Subjects with hypersensitivity to vancomycin or linezolid
6) Subjects infected with bacteria that are resistant to vancomycin or linezolid
7) Subjects with a history of hypersensitivity to peptide antibiotics or aminoglycosides
8) Subjects who are currently receiving or have received monoamine oxidase (MAO) inhibitors within 14 days prior to the first administration of the investigational product
9) Subjects who are currently receiving serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), meperidine, or buspirone
10) Subjects who are severely immunocompromised (e.g., severe neutropenia (absolute neutrophil count (ANC) $<0.5\times10^9$/L))
11) Subjects who, in the opinion of the investigator, are expected to die within 2 days from the severe complications of MRSA bacteremia

Other

12) Body Mass Index (BMI) ≥35 kg/m^2
13) Subjects who are unable to administer medication orally
14) Pregnant or lactating subjects or women and men of childbearing potential who are unwilling to use appropriate contraceptive methods* during the study period and for 14 days after the last administration of the investigational product.

    * Contraceptive methods: Use of at least one barrier method (e.g., implants, injections, oral contraceptives, intrauterine devices (IUDs)) in combination with hormonal IUDs, absolute abstinence, or vasectomy (subjects must consent to the use of at least two contraceptive methods). However, periodic abstinence (e.g., ovulation cycle, symptothermal, or post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

15) Subjects who have received other investigational products within 30 days prior to screening

16) Other subjects who, in the medical judgment of the investigator, are not suitable for participation in this study

5.2.3 Subject Withdrawal Criteria

The investigator must record the completion status of all subjects participating in the study and document the reason if administration of the investigational product or observation is discontinued. Subjects may discontinue investigational product administration or follow-up if any of the following occurs:

① Voluntary withdrawal of consent by the subject.

② When it is judged by the investigator that it is difficult to conduct further clinical trials due to adverse reactions and adverse drug reactions

③ When the subject's condition is deteriorating and the investigator determines that it is difficult to conduct further clinical trials (shock, cardiopulmonary resuscitation, ventilator treatment, etc.)

④ If the following treatment failure criteria are met during treatment period

- The investigator determines that a switch to another antibiotic for the treatment of MRSA bacteremia is required after at least 7 days of vancomycin administration (however, if vancomycin was deemed ineffective during the treatment period, a switch to daptomycin was allowed at the discretion of the investigator. After at least 14 days of vancomycin therapy (including switching to daptomycin), an oral antibiotic (excluding oxazolidinones) may be administered at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.)
- New infections other than MRSA or secondary infections resulting from MRSA bacteremia requiring treatment are identified after the first administration of the investigational product.
- Confirmed decreased susceptibility to vancomycin.

⑤ When the pregnancy of the subject is confirmed during administration of the clinical investigational drug

⑥ When investigators decide that the subject should stop participating in the trial for other reasons

Subjects who meet the above criteria and discontinue treatment with the investigational product will undergo the scheduled EOT visit within +2 days of the last administration of the investigational product or the decision to discontinue treatment, and will be considered withdrawn. However, in this case as well, subjects who discontinue treatment, with the exception of those who voluntarily withdraw consent, will undergo the TOC visit 28 days (±4 days) after the EOT visit to complete the study. No further assessments will be conducted after the completion of this study.

6 Study Design

6.1 Study Period

The total study period is approximately 24 months from the date of the IRB approval and can change depending on subject enrollment rates.

Duration for each subject: Up to 75 days

- Screening period: Up to 5 days
- Treatment period: Up to 42 days
- Treatment evaluation period: 28 days

6.2 Study Group and Control Group

At the randomization visit (Day 1), the inclusion and exclusion criteria are finally confirmed, and if subjects are eligible for this study, they are finally enrolled and randomized in a 1:1 ratio to either the study group or the control group, receiving the corresponding investigational product for up to 42 days (at least 14 days).

Treatment Group	Investigational Product	Concomitant Administration
Study group	LCB01-0371 P.O, BID	Vancomycin IV
Control group	Placebo of LCB01-0371 P.O, BID	Vancomycin IV

6.3 Randomization and Blinding

6.3.1. Randomization

Subjects who have provided written consent to participate in this study will be assigned a screening number in the order of written consent. Subsequently, subjects who meet all inclusion/exclusion criteria will be assigned a randomization number via the Interactive Web-based Response System (IWRS) in the order in which the investigator determines subject enrollment on Day 1. The method of randomization number assignment is described in detail in a separate randomization plan document.

This study will be conducted as a double-blind study. To ensure double-blinding, randomization will be performed by an independent statistician using the PLAN procedure (Proc Plan procedure) in SAS® (Ver. 9.4 or higher, SAS Institute, Cary, NC, USA) to generate a randomization list and an investigational product packaging list. The generated randomization list and investigational product packaging list will be provided to the IWRS developer and the person in charge of the investigational product packaging. The verification of the randomization numbers and the numbers of the investigational products will be conducted by the IWRS.

Randomization will be performed in a 1:1 ratio to the study group and the control group only for subjects who meet the inclusion criteria, do not fall under the exclusion criteria, and are deemed suitable for this study. A stratified block randomization method will be used for randomization, with the study site as a stratification factor.

The sponsor’s personnel responsible for packaging the investigational products must package the study and control groups appropriately and label the numbers of the investigational products in accordance with the investigational product packaging list during packaging and labeling of the investigational products.

The investigator shall obtain randomization numbers in the order of participation for subjects who meet inclusion/exclusion criteria through the IWRS, confirm the unique investigational product numbers for each subject through the IWRS, and prescribe the investigational products as assigned.

The investigator, subjects, trial pharmacists, and study personnel must remain blinded until the completion of this study. If unblinding is required during the study, it will be performed according to the procedures described in Section 6.4.2 of this protocol.

6.4 Blinding

6.4.1. Methods for Maintaining Blinding

This study is a randomized, double-blind, multicenter, parallel-design, Phase 2a study and will be conducted as a double-blind study to exclude subjective judgment of subjects and investigators.

After randomization, a placebo with the same dosage form and appearance will be used to blind the subjects and the investigator to the type of drug assigned to each subject, and the dispensing packaging will also be kept identical to ensure double-blinding. The double-blinding of the investigator and subjects will prevent bias in the assessment of therapeutic effect and AEs by the investigator or subjects. Blinding is a crucial factor for the integrity of this study. The general principle of blinding to ensure the scientific integrity of the study is to maintain the blinding of treatment allocation information (information about assigned treatment groups) for all individuals directly involved in the study until database lock and archiving. Accordingly, this general principle of blinding will be maintained until the end of the study. Database lock (DBL) and unblinding can be performed after completion of the study, followed by the preparation of the clinical study report.

To ensure double blinding, randomization numbers and investigational product codes will be used during randomization so that subjects can only be identified by their randomization numbers. The randomization list and the investigational product packaging details for each group will only be disclosed after unblinding.

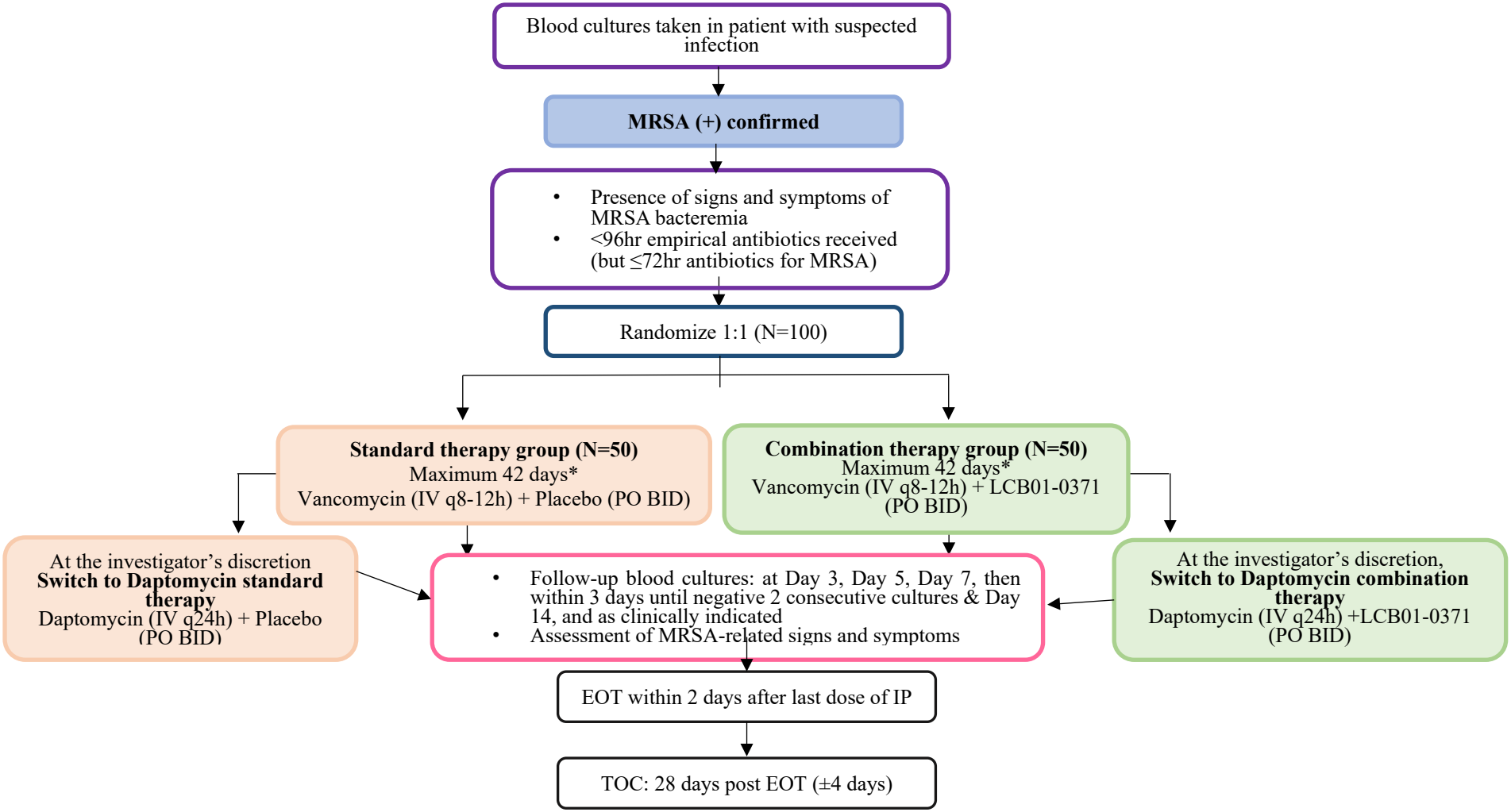
6.4.2. Unblinding

During the study period, unblinding of individual subjects is permitted only in medical emergency situations if identification of the investigational product administered is considered crucial to the subject's medical treatment. The investigator must determine whether information about the administered investigational product is important to the subject's treatment decision making before unblinding the subject's treatment status.

If unblinding is deemed necessary for reasons such as the occurrence of emergency situations that jeopardize the subject's safety, the investigator must immediately notify the sponsor (LegoChem Biosciences, Inc.) or the contract research organization (CRO) monitor delegated by the sponsor. The monitor who receives this information is required to contact the sponsor's personnel immediately. After receiving the relevant information, the sponsor's personnel will consult with the investigator to decide whether unblinding is required and document this decision. After consulting with the sponsor, the investigator will access the unblinding screen on the randomization web page, enter the required information, obtain the investigational product information for the relevant subject, print and sign the unblinding completion notification email, and retain it in the investigator's file. In cases where immediate contact with the sponsor is not possible, the investigator must follow the same procedure for unblinding, inform the sponsor of the unblinding as soon as possible, and document the reason for unblinding without consulting the sponsor. If the investigator becomes aware of a subject's randomization code information during the study period, the investigator must make every effort to exclude bias in the evaluation of efficacy and safety.

Upon completion of the study, the database will be locked once it has been confirmed to be complete and accurate, and the randomization code information will be disclosed upon the sponsor's approval for unblinding.

6.5 Study Schema



* The duration of treatment will be determined by the investigator's judgement based on the patient's condition and clinical practice guidelines for the treatment of MRSA bacteremia. After administration of vancomycin (including switch to daptomycin) for at least 14 days, vancomycin can be changed to oral antibiotics other than oxazolidinones determined by the investigator's judgement.

7 Criteria for Study Termination and Early Discontinuation

7.1 Study Termination Criteria

Termination of this study is defined as the end of the study (completion or withdrawal) of the last subject enrolled in the study.

In this study, the “EOS visit” is defined as the TOC visit at which the treatment evaluation is completed, and subjects who complete this visit are defined as “completed subjects”.

The study is considered incomplete in the following cases:

- If there are subjects in the study site who have not completed the visit schedule specified in the study.

7.2 Early Discontinuation Criteria

If, based on the results observed during the study, the investigator reasonably determines that it is not appropriate to continue the study, the investigator may, in consultation with the sponsor, terminate the study in whole or in part. In addition, the sponsor may suspend the study in whole or in part for safety or management reasons. Cases in which there is new information regarding the investigational product that indicates a negative direction in terms of the benefit-risk ratio for the subjects, including but not limited to the following reasons:

- If there is an evidence that the investigational product is ineffective
- Occurrence of new and importance adverse drug reactions or if the incidence and severity of the expected adverse drug reactions are judged to exceed expectations
- Other safety reasons
- If the sponsor determines that the continuation of the study is not justified from a medical and ethical point of view
- If it is determined that the subject enrollment rate at the study site will significantly disrupt the enrollment schedule required for this study
- If the supply of the investigational product is discontinued

If the sponsor terminates or temporarily suspends the study, the investigator must immediately notify the Institutional Review Board and submit a detailed explanation for the early termination or temporary suspension.

If the study is terminated early or suspended, the investigator must immediately inform the subject of this circumstance so that appropriate measures and follow-up can be taken.

The principal investigator shall organize the eCRF, the status of the study, and the results for the subjects up to the time of discontinuation and deliver them to the sponsor, and return the investigational product and all data related to the study to the sponsor.

8 Information and Management of Investigational Products and Concomitant Medication

8.1 Overview of the Investigational Product and Concomitant Medication

8.1.1 Study Drug

1) Code name: LCB01-0371
2) Formulation and appearance: White or off-white, oblong, film-coated tablet
3) Active ingredient: LCB01-0371 400 mg per tablet (in 715 mg)
4) Storage condition: Store in a tight container at room temperature (1-30 ℃).

8.1.2 Control Drug (Placebo)

1) Code name: Placebo of LCB01-0371
2) Formulation and appearance: White or off-white, oblong, film-coated tablet
3) Ingredient and content: A matching placebo that has the same formulation and appearance as LCB01-0371
4) Storage condition: Store in a tight container at room temperature (1-30 ℃).

8.1.3 Concomitant Medication

Vancomycin hydrochloride (including daptomycin, if applicable)*

* Drugs with the same active ingredient are allowed regardless of brand name.

Vancomycin (including daptomycin, if applicable) is used as a prescribed drug at the study site, and drugs with the same active ingredient are allowed regardless of brand name. Administration information (dosage, duration, etc.) of vancomycin and daptomycin will be collected in this study.

Oral antibiotics (excluding oxazolidinones)**

** Drugs with the same active ingredient are allowed regardless of brand name.

After at least 14 days of treatment with vancomycin (including switching to daptomycin), subjects may be switched to oral antibiotics other than oxazolidinones (e.g., rifampin, fluoroquinolones) as determined by the investigator. Information on the administration (dosage, duration, etc.) of the corresponding oral antibiotics will be collected in this study.

8.2 Manufacture, Packaging, and Labeling of the Investigational Product

The investigational product will be manufactured, packaged, and supplied to the study sites by the sponsor. The labeling of the investigational product will comply with Article 8.4 of the Good Manufacturing Practice for Investigational Medicinal Products in [Annex 4-2] of the Regulation on Safety of Pharmaceuticals, Etc. (partially amended on 08 Mar 2021, Ordinance of the Prime Minister No. 1683) and Article 7.7 of the Good Manufacturing Practice for Investigational Medicinal Products in [Annex 11] of the Regulation on Pharmaceutical Manufacturing and Quality Control (partially amended on 07 Sep 2020, MFDS Notification No. 2020-82) and will include the following information:

① A statement that it may only be used for clinical trial purposes (e.g., “for investigational use only”)
② Name or identification of the investigational product
③ Batch or code numbers to identify the contents and packaging process
④ Name, address, and phone number of the sponsor (IND holder)

⑤ Shelf-life (expiry date)
⑥ Storage conditions
⑦ Reference code to identify the study (Protocol No.)
⑧ Subject identification numbers (randomization number), investigational product numbers

8.3 Storage and Dispensing of the Investigational Product

The investigational products shall be stored in a separate, locked location at the study site to which only authorized personnel (trial pharmacist or principal investigator or study personnel managing the investigational products, hereinafter referred to as "trial pharmacist, etc.") shall have access. The trial pharmacist shall ensure an appropriate temperature in a suitable storage location to ensure proper storage of the investigational products and maintain a storage temperature log. In addition, the trial pharmacist shall comply with the shelf life (expiry date) of the investigational products and store and manage the investigational products to ensure that they are not used for purposes other than clinical studies.

8.4 Accountability, Recovery, and Disposal of the Investigational Product

The sponsor shall complete the manufacture and packaging of the investigational products and supply them to the trial pharmacist at the study site. The clinical trial pharmacist must obtain and retain a receipt for the investigational products and must store and manage the investigational products to ensure that they are not used for purposes other than clinical studies. During the conduct of the study, the sponsor must check the quantity and storage conditions of the investigational products, etc., and take measures to ensure that the study can be conducted properly. In addition, if the sponsor suspends or terminates the study, unused investigational products shall be recovered and disposed of.

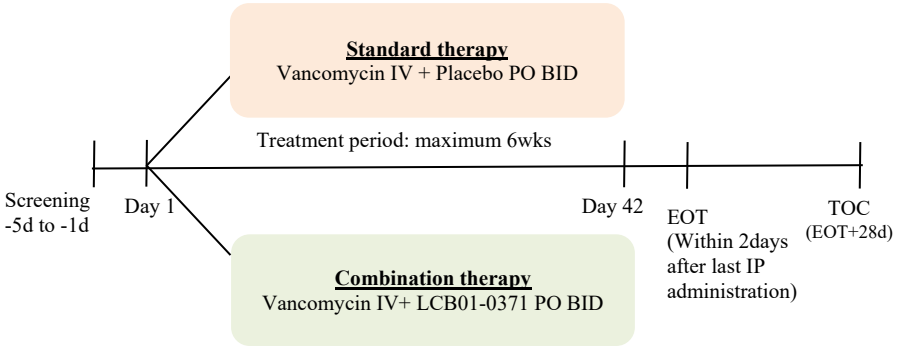
9 Study Methodology and Dosing Plan

9.1 Overall Study Methodology

This study is a Phase 2a, randomized, double-blind, multicenter, parallel design study to evaluate the efficacy, safety, and pharmacokinetic properties of LCB01-0371 with vancomycin versus vancomycin standard therapy in patients with MRSA bacteremia.

Subjects will voluntarily provide written consent to participate in this study, and screening tests and procedures will be performed. Subjects who have started empirical antibiotic therapy (e.g., vancomycin) within 72 hours prior to administration of the investigational product are eligible for enrollment. Those who have at least one positive MRSA blood culture and meet the inclusion and exclusion criteria will be enrolled in the study. Subjects will then be randomized in a 1:1 ratio to either the study group (LCB01-0371 and vancomycin combination) or the control group [standard vancomycin therapy (placebo of LCB01-0371 and vancomycin combination)]. The randomized subjects can receive the investigational product according to their assigned group for up to 42 days (at least 14 days). If the investigator determines that a switch to an antibiotic other than vancomycin is necessary for the treatment of MRSA bacteremia after initiation of therapy, a switch to daptomycin is allowed. After at least 14 days of vancomycin therapy (including switching to daptomycin), an oral antibiotic (excluding oxazolidinones) can be administered at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.

As the subjects are hospitalized, they will undergo scheduled examinations and procedures, including pharmacokinetic assessments, at each time point. Upon completion of the administration of the investigational product, subjects will attend the EOT and test of cure (TOC) visits for tests and procedures to evaluate efficacy and safety.



Study Schema

9.2 Dosage and Administration Method of the Investigational Product

9.2.1 Dosage and Treatment Period

1) Treatment period: Up to 42 days (at least 14 days)

   * The treatment period will be determined based on the subject's condition and the investigator's judgment according to the guidelines for the treatment of MRSA bacteremia and may be administered for up to 6 weeks (at least 14 days).

2) Dosage and administration method:

Treatment Group	Investigational Product			Concomitant Medication*
		Morning	Evening	
Study group	Single dose of two tablets of LCB01-0371	●●	●●	Vancomycin (IV)
Control group	Single dose of two tablets of placebo of LCB01-0371	○○	○○	Vancomycin (IV)
●: LCB01-0371 400 mg				
○: Placebo of LCB01-0371 400 mg				

* Switching to daptomycin: After at least 7 days of vancomycin administration, subjects may be switched to daptomycin if deemed necessary by the investigator for the treatment of MRSA bacteremia. See "③ Daptomycin" for dosage and administration of daptomycin. In addition, subjects may be switched to oral antibiotics, except for the oxazolidinones, based on investigator judgment after at least 14 days of vancomycin administration (including a switch to daptomycin). Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.

① LCB01-0371: 2 tablets per dose, administered orally twice daily (morning and evening)

② Vancomycin: Initial dose of 15-20 mg/kg, administered intravenously q8h-q12h (assuming MIC_{BMD} = 1 mcg/mL), with subsequent dose adjustments to maintain the vancomycin concentration at an AUC/MIC_{BMD} ratio of 400-600 (see 2020 Infectious Diseases Society of America (IDSA) guidelines[20]).

The investigator can adjust the vancomycin dosage and treatment regimen based on the subject's renal function according to the approved vancomycin labeling and therapeutic drug monitoring (TDM) results.

*According to the 2020 IDSA guidelines, the recommended dosage and administration of vancomycin for patients with normal renal function is 15-20 mg/kg administered intermittently at q8h-q12h intervals. According to the 2020 IDSA guidelines, monitoring of the PK/PD parameter AUC/MIC ratio is recommended for patients with severe MRSA infections to maintain effective vancomycin blood concentrations and minimize nephrotoxicity. Assuming that the MIC_{BMD} is 1 mcg/mL, vancomycin is considered to achieve optimal effective blood concentrations when maintained at an AUC/MIC_{BMD} ratio of 400-600. The first follow-up is conducted preferably within the first 24-48 hours after the start of treatment. The frequency of monitoring should be determined based on clinical judgment (e.g., weekly for hematologically stable patients, more frequently or daily for unstable patients).

③ Daptomycin: 6-10 mg/kg, q24h, IV injection. The investigator may adjust the dosage and administration of daptomycin according to the approved labeling based on the subject's renal function.

④ Oral antibiotics (excluding oxazolidinones): After at least 14 days of treatment with vancomycin (including switching to daptomycin), subjects may be switched to oral antibiotics other than oxazolidinones at the discretion of the investigator. The dosage and administration of each oral antibiotic will follow the approved labeling for MRSA treatment.

9.3 Concomitant Medication/Therapy

9.3.1 Permitted Concomitant Medication and Therapy

The following medications and treatments are allowed during the study period (from the first administration of the investigational product to the completion of the TOC visit, as specified in the protocol).

1) Medications other than contraindicated combinations may be administered during the study at the discretion of the investigator, provided the dosage remains stable.
2) Temporary medications and treatments for symptom control due to MRSA bacteremia are allowed, except for antibiotics specifically used to treat MRSA bacteremia.
3) Daptomycin: After at least 7 days of vancomycin administration, subjects can be switched to daptomycin if deemed necessary by the investigator for the treatment of MRSA bacteremia. Subjects who discontinue vancomycin and are switched to daptomycin (6–10 mg/kg, q24h h, IV) will continue scheduled visits. The investigator may adjust the dosage and administration of daptomycin according to the approved labeling based on the subject's renal function.
4) After at least 14 days of treatment with vancomycin (including switching to daptomycin), subjects may be switched to oral antibiotics other than oxazolidinones at the discretion of the investigator and continue scheduled visits.
5) Temporary administration of antibiotics for skin and soft tissue infections or urinary tract infections is allowed at the discretion of the investigator (however, linezolid and tigecycline are prohibited during the study).
6) Antiviral and antifungal agents used for prophylaxis may be administered concomitantly at the discretion of the investigator.
7) Medications for the temporary treatment of other diseases may be administered concomitantly after consultation with the investigator.

If any concomitant medications (including medications to treat other diseases or adverse events (AEs)) are administered, the investigator should record the information about the medications (product name, purpose of administration, dose, treatment period, etc.) in detail in the electronic case report form (eCRF).

9.3.2 Prohibited Concomitant Medication and Therapy

The following medications will be prohibited throughout the study.

1) Antibiotics with antibacterial activity against MRSA (e.g., rifampin, clindamycin, trimethoprim-sulfamethoxazole, doxycycline, gentamicin, linezolid, tigecycline, etc.). However, empirical antibiotics, including vancomycin, used to treat Gram-positive bacteria within 72 hours prior to randomization are allowed. In addition, after at least 14 days of treatment with vancomycin (including switching to daptomycin), subjects may be switched to oral antibiotics other than oxazolidinones at the discretion of the investigator.
2) MAO inhibitors (drugs that inhibit MAO-A or MAO-B; e.g., phenelzine, isocarboxazid, selegiline, moclobemide, etc.)
3) Selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), meperidine, buspirone

If the use of contraindicated medications was necessary or administered for the treatment of a subject during the study, the investigator should determine whether the subject's treatment should be discontinued and document the details in the e-CRF.

9.3.3 Medications to be Used with Caution

The following medications may be administered concomitantly during the study, but must be closely monitored due to possible interactions with vancomycin.

1) Medications with potential neurotoxicity or nephrotoxicity (e.g., amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, platinum-containing anticancer drugs (cisplatin, nedaplatin, etc.))
2) Anticoagulants

9.4 Treatment Compliance

The investigational product will be administered at the study site and treatment compliance will be assessed according to a separate investigational product manual. In addition, information will be collected on the administration of vancomycin (and/or daptomycin) as part of standard therapy and on oral antibiotics (with the exception of oxazolidinones) administered at the investigator's discretion.

The investigator/designee is responsible for instructing the subjects to ensure proper administration of the investigational product.

If a subject forgets to take the investigational product, they will be instructed to take the investigational product as follows.

- If the subject realizes that they have forgotten to take the investigational product before bedtime, they should take it immediately.
- If the subject realizes the missed dose after waking up the next day, they should skip the previous dose and take the scheduled dose for that day.

The treatment compliance is calculated as follows.

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

10 Study Procedures and Assessments

10.1 Observation Items

10.1.1 Informed Consent Form and Allocation of Screening Number and Enrollment Number

1) Obtaining Informed Consent Form and Assigning Screening Number

Before starting the study, the investigator shall obtain written informed consent from the subject (or the subject's representative) who wishes to participate in this study, after having fully informed him/her of the purpose and content of this study. Written informed consent must be obtained before any study procedures, and the subject must review the study information and sign the informed consent form in their own handwriting. The investigator must provide the subject with a copy of the signed consent form and the information sheet.

Screening numbers will be assigned in the order of written informed consent. If a subject who has been assigned a screening number fails the screening, that screening number will also be withdrawn and will not be reassigned to another subject.

10.1.2 Demographic Data

During the screening visit, demographic data such as age (year/month of birth), gender, etc., will be verified through interview, chart review, and questions and recorded in the eCRF.

10.1.3 Medical History

Past medical history including surgical history within 3 months prior to screening and current medical history will be examined (diagnosis, date of diagnosis, current status, etc.). In the case of malignancies, however, only data from the last 5 years will be collected. The collected medical history will also be checked for its relevance to MRSA bacteremia. For subjects with suspected endocarditis, echocardiography can be performed at the discretion of the investigator. If subjects have results of previous tests at the time of screening, these results will be taken as a medical history.

10.1.4 Prior/Concomitant Medication/Therapy

1) Prior medication

Information about medications administered to the subjects within 30 days of screening will be collected.

2) Concomitant medication/combination therapy

After the baseline visit, information on concomitant medications administered from the time points indicated in the schedule of activities, including drug names (generic names), purpose of administration, daily dosage, route of administration, and duration of treatment, will be collected and recorded in the CRF.

10.1.5 Vital Signs

Measurements will be taken at the time of screening tests, Day 1, Day 3, Day 5, and Day 7, and then at weekly intervals (Day 14, Day 21, Day 28, Day 35, Day 42), and at the EOT/DC, TOC visit. Additional measurements will be taken as deemed necessary by the investigator. If possible, vital signs should be measured before other planned examinations. Blood pressure (systolic, diastolic), pulse, temperature, and respiration should be measured after at least 5 minutes of rest.

10.1.6 Body Measurement

Height will be measured only at the time of screening. If a measurement is available before the screening, the most recent result will be collected. Body weight will be measured at screening and at the EOT/DC visits. If the data are available to two decimal places, they will be rounded to one decimal place for collection.

10.1.7 Physical Examination

Physical examination will be conducted at the time of screening tests, Day 1, Day 3, Day 5, and Day 7, and then at weekly intervals (Day 14, Day 21, Day 28, Day 35, Day 42), and at the EOT/DC, TOC visit. Additional examinations will be performed as deemed necessary by the investigator. During the physical examination, the appearance, skin, head/neck, chest/lungs, heart, abdomen, urogenital system, extremities, musculoskeletal system,

nervous system, lymph nodes, and other organs will be examined. Significant findings detected during the screening test will be recorded in the physical examination section of the eCRF, and significant changes in physical findings that meet the definition of adverse events after administration of the investigational product will be recorded in the adverse events section of the eCRF.

10.1.8 Laboratory Tests

For screening tests, with the exception of pregnancy tests, the results obtained within 1 week (7 days) prior to screening may be used. However, for clinically significant abnormal results, the laboratory tests should be performed at the screening visit as well.

Hematology, blood chemistry, and urinalysis will be performed at screening and on Day 1, Day 7, and every week thereafter with the following laboratory tests. Blood coagulation tests will be performed at screening and at the EOT visit. Additional tests may be performed as deemed necessary by the investigator. At the EOT visit, the test can be omitted if the results of the previous 3 days are available. For women of childbearing potential, serum or urine pregnancy tests will be performed at screening, and participation is allowed if the result is negative. Further pregnancy tests can be performed at the discretion of the investigator. The laboratory tests include the following test items.

Table 2. Laboratory Test Items

Laboratory Tests	Test Items	Collection Volume
Hematology	RBC, hemoglobin, hematocrit, platelet, ANC, WBC, WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Blood: About 15 mL per collection Urine: About 15 mL per collection
Blood chemistry	albumin, total protein, alkaline phosphatase, ALT, AST, γ-GT [a),b)], total bilirubin, blood urea nitrogen (BUN), creatinine, uric acid, glucose, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), phosphorus (P), C-reactive protein (CRP), creatine phosphokinase (CPK)[a)], triglyceride [a),b)]	
Coagulation[c)]	PT (INR), aPTT	
Urinalysis	pH, occult blood, glucose, albumin (protein), urine microscopy (RBC, WBC), bacteria	
Pregnancy test	Serum or urine HCG (only for women of childbearing potential)	

a) These tests are not performed at the screening visit.
b) The tests are performed on Day 1, Day 14, and at the EOT visit. At the EOT visit, the test can be omitted if the results of the previous 3 days are available.
c) These tests are performed at screening and at the EOT visit.

10.1.9 12-Lead ECG

The electrocardiogram examination will be performed using a 12-lead ECG at screening and at the EOT visit. Additional examinations will be performed as deemed necessary by the investigator. For screening tests, the results obtained within 3 days prior to screening may be used. However, for clinically significant abnormal results, the tests should be performed at the screening visit as well.

The results of the ECG evaluation and the determination of normal/abnormal will be recorded in the eCRF. Clinically significant abnormal results at screening will be recorded in the medical history section of the eCRF, and clinically significant abnormal results after administration of the investigational product will also be recorded in the adverse events section of the eCRF.

10.1.10 Blood Culture

For blood cultures, two sets of blood cultures will be collected from different sites if possible and performed consecutively (1 set = 2 bottles; 1 anaerobic and 1 aerobic, approximately 20 mL per set). According to the inclusion criteria, at least one positive MRSA test result is required before randomization.

Blood cultures performed for MRSA confirmation at screening can be based on results obtained during routine medical care prior to obtaining consent. However, the test results must be obtained either within 72 hours prior to randomization or within 96 hours prior to randomization if empirical treatment with vancomycin is initiated within 72 hours (compliance with inclusion criterion 2). The identification of MRSA can also be confirmed by rapid test results from each study site.

Blood cultures will be performed at screening, on Day 3, Day 5, and Day 7, and then every 3 days until MRSA results are confirmed negative twice consecutively (i.e., if the first negative result is obtained, the second test will be performed within 3 days to confirm the second negative result). The blood cultures will also be performed on Day 14 and at the EOT visit. If the MRSA results are confirmed negative twice consecutively before the EOT visit, no blood cultures will be performed at the EOT visit. Additional tests may be performed as deemed necessary by the investigator.

10.1.11 Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) is defined as the lowest concentration of the antibiotic that inhibits microbial growth in in vitro sensitivity tests and serves as an indicator for measuring the antimicrobial activity of the antibiotic. Evaluation of the MIC of vancomycin is performed after the screening at the investigator's discretion to confirm susceptibility, determine resistance to MRSA, and adjust the vancomycin dose. In addition, MIC_{BMD} analysis can be performed at a designated laboratory by transferring samples when necessary. The resistance criteria for vancomycin follow the Clinical and Laboratory Standards Institute (CLSI) M100-S27 (2017) guidelines[21] (see Table 3). To confirm the resistance of LCB01-0371 to MRSA, the MIC of LCB01-0371 will be analyzed on Day 14 in subjects whose blood culture results are not negative conversion by Day 14 after screening. In subjects who discontinue treatment before Day 14 or whose blood cultures are not negative conversion by the EOT visit, the MIC of LCB01-0371 will be evaluated at the EOT visit. However, this evaluation will be performed only when possible and at a designated laboratory.

Table 3 Antibiotic Resistance Criteria for Staphylococcus Aureus (Based on CLSI (M100-S27, 2017) Guidelines)

Classification	MIC		
Vancomycin	Susceptible	Intermediate	Resistant
	≤2	4-8	≥16

10.1.12 Efficacy Assessment

Efficacy assessment will be conducted on Day 3, Day 5, Day 7, Day 14, at the EOT visit, and at the TOC visit, which includes evaluation of clinical symptoms and signs of MRSA bacteremia, review of blood culture results, determination of MRSA bacteremia relapse, and occurrence of death.

10.1.13 PK Assessment

Blood samples will be collected for PK assessment at the following time points.

No.	Day	Blood sampling time point	No.	Day	Blood sampling time point	Collection volume (mL)
1	1	30min-1h	3	from Day 3 to EOT	30min-1h	8 mL
2		2h-8h	4		2h-8h	8 mL

10.1.14 Randomization and Administration of the Investigational Product

Subjects in whom at least one set of blood cultures tested positive for MRSA within 72 hours prior to randomization or subjects in whom at least one set of blood cultures tested positive for MRSA within 96 hours prior to randomization and who started treatment with vancomycin at least 72 hours prior to randomization may be enrolled in this study. Subsequently, the subjects will be randomized to the study group or the control group to receive the investigational product from Day 1 and up to 42 days (at least 14 days).

Detailed information can be found in Section 9.2.

10.1.15 Symptoms and Signs of MRSA Bacteremia

Signs and symptoms related to MRSA bacteremia are indicators for assessing clinical improvement and the success/failure of treatment. Therefore, the primary lesion of MRSA infection, the status of removal of the primary

lesion of MRSA infection, and the infection reactions related to bacteremia from screening to the end of the study will be recorded separately as “MRSA infection-related signs and symptoms”. However, complications due to bacteremia will be collected as a single diagnosis that includes clinical symptoms, laboratory tests, vital signs, or other related reactions (e.g., endocarditis). Symptoms and signs related to the exacerbation of primary lesions from MRSA infection and bacteremia following the administration of the investigational product will be collected as AEs related to “MRSA bacteremia”.

10.1.16 Adverse Events

Any clinically significant medical conditions or abnormalities observed in subjects from the administration of the investigational product until the end of the study will be collected as AEs. Any clinically significant abnormal findings observed on vital signs, physical examination, laboratory tests, electrocardiogram examination, and other safety assessments will be collected as adverse events. Any AEs confirmed before administration of the investigational product will be collected as new AEs if their severity worsens after administration. Adverse events will be evaluated for their causal relationship with the investigational product LCB01-0371 and for a relationship with other than LCB01-0371 (concomitant medications and therapies, MRSA bacteremia, underlying diseases other than MRSA, none, unknown, other, etc.).

The criteria for the evaluation of adverse events and the reporting procedures can be found in Section 10.5.

10.2 Visit Schedule

10.2.1 Screening Visit (Within 5 Days of the Baseline Visit)

The screening visit and Day 1 can be performed on the same day.

The following procedures will be performed to confirm the subject’s eligibility.

1) Prior to the start of any study procedures, subjects will be informed about the study procedures and written informed consent form will be obtained.
2) Screening numbers will be assigned to the subjects.
3) Demographic data, past and current medical history, and prior medications will be examined.
4) Vital signs (systolic/diastolic blood pressure, pulse rate, temperature, and respiratory rate) will be measured.
5) Body measurement (height and weight): Height will be measured only at the time of screening. If a measurement is available before the screening, the most recent result will be collected.
6) Physical examination will be performed.
7) Laboratory tests will be performed. (however, pregnancy tests will be performed only for women of childbearing potential).
8) 12-lead ECG will be performed.
9) Blood cultures will be performed (can be based on the results obtained during routine medical care prior to obtaining consent. However, the test results must be obtained either within 72 hours prior to randomization or within 96 hours prior to randomization if empirical treatment with vancomycin is initiated within 72 hours [compliance with inclusion criterion 2]).
10) MIC evaluation for vancomycin and LCB01-0371 (optional) will be conducted.
11) Symptoms and signs related to MRSA bacteremia will be collected.

10.2.2 Treatment Visit (Day 1 [Baseline Visit], Day 3, Day 5, Day 7, Day 14, Day 21, Day 28, Day 35, Day 42)

The screening visit and Day 1 (baseline visit) can be performed on the same day. Administration of vancomycin/investigational product is recommended as soon as possible after randomization.

1) After reconfirmation of the inclusion/exclusion criteria, the subjects will be assigned randomization numbers. The results of the laboratory tests at the screening visit will be used to confirm that the subject is suitable for

participation. Subjects in whom at least one set of blood cultures tested positive for MRSA within 72 hours prior to randomization; or subjects in whom at least one set of blood cultures tested positive for MRSA within 96 hours prior to randomization and who started treatment with vancomycin at least 72 hours prior to randomization can be enrolled in this study.

2) Past and current medical history, prior medication: On Day 1, past and current medical history as well as prior medications administered after screening, which were not collected during the screening, will be checked.
3) Vital signs (systolic/diastolic blood pressure, pulse rate, temperature, and respiratory rate) will be measured.
4) Physical examination will be performed.
5) Laboratory tests: The laboratory tests will be performed on Day 1 and Day 7 and then weekly (Day 14, Day 21, Day 28, Day 35, Day 42). Additional tests will be performed as deemed necessary by the investigator.
6) 12-lead ECG: Performed as deemed necessary by the investigator.
7) Blood cultures: Blood cultures will be performed on Day 3, Day 5, and Day 7, and then every 3 days until MRSA results are confirmed negative twice consecutively (i.e., if the first negative result is obtained, the second test will be performed within 3 days to confirm the second negative result). The blood cultures will also be performed on Day 14 and at the EOT visit. If the MRSA results are confirmed negative twice consecutively before the EOT visit, no blood cultures will be performed at the EOT visit. Additional tests may be performed as deemed necessary by the investigator.
8) MIC evaluation: Evaluation of the MIC of vancomycin will be performed at the investigator's discretion to determine resistance to MRSA and adjust the vancomycin dose. In addition, MIC_{BMD} analysis can be performed at a designated laboratory by transferring samples when necessary. Evaluation of the MIC of LCB01-0371 will be performed on Day 14 only in subjects whose blood culture results are not negative conversion by Day 14 and at the EOT visit in subjects who discontinue the treatment before Day 14. However, this evaluation will be performed only when possible and at a designated laboratory.
9) Efficacy assessment: Efficacy assessment will be conducted on Day 3, Day 5, Day 7, Day 14, at the EOT visit, and at the TOC visit, which includes evaluation of clinical symptoms and signs of MRSA bacteremia, review of blood culture results, and occurrence of death.
10) PK assessment: PK assessments will be performed after administration of the investigational product on Day 1 and after Day 3 (before the end of treatment).
11) The investigational product and vancomycin will be administered. If the investigator determines that a switch to an antibiotic other than vancomycin is necessary for the treatment of persistent MRSA bacteremia after at least 7 days of vancomycin administration, a switch to daptomycin is allowed. After at least 14 days of vancomycin therapy (including switching to daptomycin), an oral antibiotic (excluding oxazolidinones) can be administered at the discretion of the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.
12) Concomitant medication/combination therapy will be collected.
13) Symptoms and signs related to MRSA bacteremia will be collected.
14) Adverse events will be checked.

10.2.3 EOT/DC Visit (+2 Days)

This visit should be conducted within +2 days of the last administration of the investigational product or the decision to withdrawal, and the following procedures will be performed at this visit.

1) Vital signs (systolic/diastolic blood pressure, pulse rate, temperature, and respiratory rate) and body weight will be measured.
2) Physical examination will be performed.
3) Laboratory tests and 12-lead ECG will be performed.
4) Blood cultures: If the MRSA results are confirmed negative twice consecutively before the EOT visit, no blood cultures will be performed at the EOT visit. However, additional tests can be performed as deemed necessary by the investigator.
5) Evaluation of the MIC of vancomycin and LCB01-0371 (optional): Evaluation of the MIC of vancomycin

will be performed as deemed necessary by the investigator. In addition, MIC_{BMD} analysis can be performed at a designated laboratory by transferring samples when necessary. Evaluation of the MIC of LCB01-0371 will be performed only in subjects who discontinue the treatment before Day 14 and those whose blood culture results are not negative conversion by EOT. This evaluation will be performed only when possible and at a designated laboratory.

6) Efficacy assessment: Clinical signs and symptoms of MRSA bacteremia will be evaluated and blood culture results will be confirmed.
7) Concomitant medication/combination therapy will be collected.
8) Symptoms and signs related to MRSA bacteremia will be collected.
9) Adverse events will be checked.

10.2.4 TOC Visit ((EOT +28 Days) ± 4 Days)

This visit will be conducted 28 days (±4 days) after the EOT visit or DC visit to assess continued clinical response and for the safety follow-up, and the procedures for this visit are as follows.

1) Vital signs (systolic/diastolic blood pressure, pulse rate, temperature, and respiratory rate) and body weight will be measured.
2) Physical examination will be performed.
3) Laboratory tests and 12-lead ECG: Performed as deemed necessary by the investigator.
4) Blood cultures: Performed as deemed necessary by the investigator.
5) Efficacy assessment: Clinical signs and symptoms of MRSA bacteremia will be evaluated and recurrence of MRSA bacteremia will be determined.
6) Concomitant medication/combination therapy will be collected.
7) Symptoms and signs related to MRSA bacteremia will be collected.
8) Adverse events will be checked.

10.2.5 Unscheduled Visit

If a subject visits the study site on an unscheduled date as medical treatment is required due to test results or adverse events during the study, these circumstances must be recorded in the relevant forms. The planned site visit schedule must not be changed due to unscheduled visits.

10.3 Efficacy Assessment

10.3.1 Efficacy Endpoints and Assessment Methods

1) Primary Endpoint

Proportion of subjects with overall cure on Day 14 of treatment (composite response rate): 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)[a].

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

The proportion of subjects with overall cure (composite response rate) is calculated as follows.

Composite response rate (%) = (number of subjects with overall cure within 14 days / number of subjects in the efficacy analysis set) * 100

2) Secondary Endpoints

① Proportion of subjects with overall cure by the EOT visit (composite response rate)

Composite response rate (%) = (number of subjects with overall cure by the EOT visit / number of subjects in the efficacy analysis set) * 100

② Mortality due to MRSA bacteremia during the treatment period with the investigational product

Mortality due to MRSA bacteremia during the treatment period = (number of subjects who died of MRSA bacteremia during the treatment period after starting the administration of the investigational product / number of subjects in the efficacy analysis set) * 100

③ Relapse rate of MRSA bacteremia

: Proportion of subjects with relapse MRSA bacteremia after two consecutive negative MRSA test results and prior to the TOC visit

Relapse rate of MRSA bacteremia = (number of subjects with a relapse of MRSA bacteremia after clearance of bacteremia up to the TOC visit / number of subjects with clearance of bacteremia) * 100

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 on Day 3, Day 5, Day 7, Day 14 and at the EOT visit)

Clearance rate = (number of subjects with clearance of bacteremia on Day 3, Day 5, Day 7, Day 14 and at the EOT visit* / number of subjects in the efficacy analysis set on Day 3, Day 5, Day 7, Day 14 and at the EOT visit) * 100

* 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.

⑤ Proportion of subjects with persistent MRSA bacteremia based on blood culture results on Day 3, Day 5, Day 7, and Day 14

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

- Proportion of subjects with persistently positive MRSA blood cultures up to Day 3 = (number of subjects with the first positive MRSA result before randomization and positive MRSA results on Day 3 / number of subjects in the efficacy analysis set on Day 3) * 100
- Proportion of subjects with persistently positive MRSA blood cultures up to Day 5 = (number of subjects with the first positive MRSA result before randomization and positive MRSA results on Day 3 and Day 5/ number of subjects in the efficacy analysis set on Day 5) * 100
- Proportion of subjects with persistently positive MRSA blood cultures up to Day 7 = (number of subjects with the first positive MRSA result before randomization and positive MRSA results on Day 3, Day 5, and Day 7 / number of subjects in the efficacy analysis set on Day 7) * 100
- Proportion of subjects with persistently positive MRSA blood cultures up to Day 14 = (number of subjects with the first positive MRSA result before randomization and positive MRSA results on Day 3, Day 5, Day 7, and Day 14 / number of subjects in the efficacy analysis set on Day 14) * 100

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.

Definition of Clinical Outcome	
Clinical improvement	Disappearance of the symptoms of infection existing at the time of enrollment in the study, **without** new infections or new secondary infections caused by MRSA.
Clinical failure	Subjects who experience clinical failure during the treatment period will be considered treatment failures for the remainder of the study. The following cases are classified as clinical failure if any of the following criteria are met. ✓ Death due to MRSA bacteremia during the treatment period with the investigational product ✓ A switch to another antibiotic for the treatment of MRSA bacteremia is required (however, if the treatment with vancomycin fails during the treatment period, a switch to daptomycin is allowed at the discretion of the investigator. After at least 14 days of vancomycin administration (including switching to daptomycin), it can be switched to an oral antibiotic (excluding oxazolidinones) at the discretion of

	the investigator. Subjects who are switched to another antibiotic according to the above criteria will continue scheduled visits.) ✓ New infections other than MRSA or secondary infections resulting from MRSA bacteremia requiring treatment are identified.
Definition of Microbiological Outcome	
Clearance of MRSA bacteremia	Two consecutive negative MRSA blood cultures.
Persistent MRSA bacteremia	Persistent MRSA positivity in blood cultures.
MRSA bacteremia relapse	Relapse of MRSA bacteremia after two consecutive negative MRSA test results and before the TOC visit

10.4 Safety Assessment

Safety assessment will be conducted through monitoring of subjective and objective adverse events, vital signs, physical examination, laboratory tests (hematology/blood chemistry/coagulation/urinalysis), and ECGs.

10.4.1 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) Abnormal changes in vital signs, electrocardiogram (ECG), laboratory tests, and physical examination

10.4.2 Safety Assessment Methods

1) Adverse Events

AE refers to any symptoms, signs, or abnormal laboratory test results that occur or worsen after administration of the investigational product. The type, date of onset and end, severity, treatment and outcome, causal relationship with the investigational product, and causal relationship with factors other than the investigational product will be recorded in the AE section of the e-CRF. AEs will be categorized and summarized as those related to the investigational product and those not related to the investigational product (such as concomitant medications and therapies, MRSA bacteremia, underlying diseases other than MRSA, none, unknown, or other related AEs). All AEs will be coded and classified by system organ class (SOC) and preferred term (PT) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). For detailed information on adverse event evaluation criteria, evaluation methods, and follow-up, see Section 10.5.

2) 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

Mortality due to exacerbation of MRSA bacteremia at the time of the TOC visit = (number of subjects who died after administration of the investigational product up to the TOC visit / number of subjects in the safety set) * 100

3) Incidence of thrombocytopenia

Proportion (%) of subjects with thrombocytopenia after administration of the investigational product

4) Vital signs

Vital signs are measured at each visit whenever possible before other scheduled tests are performed. After resting for at least 5 minutes, the subjects' systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate will be measured in a sitting position.

Abnormal findings in vital signs that meet the definition of an abnormality should be reported as AEs. However, not all abnormal vital sign results are considered AEs. Vital sign results are reported as AEs if they meet any of the following criteria:

- Accompanied by clinical symptoms,
- Leading to a change in the administration of the investigational product (e.g., temporary interruption or permanent discontinuation),
- Leading to medical interventions or changes in concomitant therapy.

If considered clinically significant, the investigator is responsible for reviewing all vital signs and determining whether individual abnormal results should be classified as AEs based on medical and scientific judgment.

If clinically significant abnormal vital signs indicate a disease or sign of a syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded in the AE section of the e-CRF.

5) Laboratory Tests

The results of the laboratory tests are classified as normal or abnormal (not clinically significant (NCS) and clinically significant (CS)). If the laboratory test results are determined to be clinically significant after administration of the investigational product compared to before administration, it will be reported as an AE, and the findings on the abnormal values will be recorded.

Not all laboratory abnormalities are considered AEs. Laboratory abnormalities are reported as AEs if they meet any of the following criteria:

- Accompanied by clinical symptoms,
- Leading to a change in the administration of the investigational product (e.g., temporary interruption or permanent discontinuation),
- Leading to medical interventions (e.g., potassium supplementation for hypokalemia) or changes in concomitant therapy,

- If deemed clinically significant by the investigator.

The investigator is responsible for reviewing all laboratory test results and determining whether individual laboratory abnormalities should be classified as AEs based on medical and scientific judgment.

If clinically significant laboratory abnormalities indicate a disease or sign of a syndrome (e.g., bilirubin value increased with cholestasis), only the diagnosis (e.g., cholestasis) should be recorded in the AE section of the e-CRF.

If clinically significant laboratory abnormalities are not indicative of a disease or syndrome, both the abnormality and a descriptor indicating whether the result is above or below the normal range should be recorded in the AE section of the e-CRF (e.g., "potassium increased" instead of "potassium abnormal").

If laboratory abnormalities can be classified according to standard definitions using the appropriate clinical terms, these clinical terms should be recorded as AEs. For example, an increase in serum potassium level to 7.0 mEq/L should be recorded as "hyperkalemia".

6) Physical Examination and ECG

Any significant changes observed on physical examination or ECG results following administration of the investigational product that meet the definition of an AE should be reported as AEs.

10.5 Evaluation Criteria and Reporting of Adverse Events

10.5.1 Definition of Terms

1) Adverse Event (AE)

An adverse event (AE) refers to any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease that occurs in subjects who have received an investigational product, which does not necessarily have a causal relationship with the investigational product.

Adverse events that occur after treatment are referred to as treatment-emergent adverse events (TEAEs), i.e. adverse events that were not present before administration of the investigational product but occurred after administration, or adverse events that were present at baseline but worsened in severity after administration of the investigational product.

2) Adverse Drug Reaction (ADR)

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.

3) Serious AE/ADR

A serious adverse event/adverse drug reaction (SAE/SADR) refers to any of the following cases among the AEs or ADRs that occur at any dose of the investigational product.

① Results in death or is life-threatening[1]

② Requires hospitalization or prolonged hospitalization[2]

③ Results in persistent or significant disability/incapacity

④ Results in a congenital anomaly/birth defect

⑤ 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.[3]

[1]Death is included as an efficacy endpoint, and deaths due to exacerbation of complications (e.g., sepsis) caused by MRSA bacteremia will not be collected as serious adverse events. However, unexpected sudden deaths not due to causes other than complications (e.g., sepsis) resulting from MRSA bacteremia or deaths of unknown cause must be reported as serious adverse events.

[2]The following cases do not constitute "cases requiring hospitalization or prolonged existing hospitalization" and are not reported as serious adverse events:

- Hospitalization or prolongation of hospitalization for procedures (e.g., surgery, examination) that were planned prior to the study.
- Hospitalization or prolongation of hospitalization for follow-up of previously cured or improved conditions.
- Hospitalization or prolonged hospitalization for examination or education.
- Hospitalization or prolonged hospitalization for non-medical reasons (e.g., temporary absence of family members).
- Hospitalization or prolonged hospitalization in hospice facilities, nursing care facilities, or rehabilitation facilities.
- Hospitalization or prolonged hospitalization planned before signing the informed consent form

[3]Other medically important situations (e.g., acute allergic reactions) are considered serious adverse events in the medical judgment of the investigator, even if they are not immediately life-threatening or result in death or hospitalization, as they jeopardize the subject or require intervention to prevent the occurrence of such symptoms. Since this study is conducted in hospitalized patients with MRSA bacteremia, hospitalization and prolonged hospitalization due to MRSA bacteremia are not considered serious adverse events. However, prolonged hospitalization due to worsening of existing symptoms or occurrence of new symptoms after administration of the investigational product should be reported as a serious adverse event.

10.5.2 Criteria for the Evaluation of Adverse Events

10.5.2.1. Severity

The severity of adverse events is assessed according to NCI-CTCAE[22] ver 5.0. If an evaluation according to NCI-CTCAE is not possible, the following criteria will be used:

Severity	Grade	Description
Mild	1	Symptoms are barely noticeable to the subject and do not interfere with daily activities. The use of medication to alleviate the symptoms is generally not necessary.
Moderate	2	Symptoms are severe enough to cause discomfort to the subject; the subject can continue the study but may require symptomatic treatment.
Severe	3	Symptoms cause significant discomfort and may be severe enough to prevent the subject from continuing the study. The severity of symptoms may result in discontinuation of the investigational product; treatment of symptoms may be required, and/or hospitalization may be necessary.
Life-threatening (Life-threatening)	4	Symptoms caused by the adverse event may pose an immediate threat to the subject's life. This does not include more severe events but may result in death.
Death	5	Subject has died due to the adverse event.

10.5.2.2. Causal Relationship with the Investigational Product

The relationship between the administration of the investigational product and the occurrence of adverse events is determined by the investigator.

Causal Relationship	Rationale	
Related	1) Definitely	• If there is evidence that the investigational product has been administered and the temporal sequence between the administration of the investigational product and the occurrence of the adverse event is reasonable. • If the adverse event is most plausibly explained by the administration of the investigational product and not by any other reason. • If the adverse event disappears as a result of the interruption of administration. • If the result is positive following rechallenge (performed if practically feasible). • If the adverse event exhibits a pattern consistent with information already known about the investigational product or drugs in the same class.
	2) Probably, Likely	• If there is evidence that the investigational product has been administered and the temporal sequence between the administration of the investigational product and the occurrence of the adverse event is reasonable. • If the adverse event is most plausibly explained by the administration of the investigational product and not by any other reason.

Causal Relationship	Rationale	
		• If the adverse event disappears as a result of the interruption of administration.
	3) Possible	• If there is evidence that the investigational product has been administered and the temporal sequence between the administration of the investigational product and the occurrence of the adverse event is reasonable. • If the adverse event is determined to be attributable to the administration of the investigational product at the same extent as other possible causes. • If the adverse event disappears as a result of the interruption of administration (if performed).
	4) Unassessable	• If there is insufficient evidence to determine causality. • Cases in which the causal relationship cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.
Not related	1) Unlikely	• If there is evidence that the investigational product has been administered. • If there is another, more plausible cause for the adverse event. • If the result is negative or equivocal as a result of the interruption of administration (if performed). • If the result is negative or equivocal following rechallenge (if performed).
	2) Not related	• If the investigational product was not administered to the subject. • If the adverse event is not reasonably related in time to the administration of the investigational product. • If there is another obvious cause for the adverse event.

10.5.2.3. Causal Relationship with Other Than the Investigational Product

Causal relationship with other than the investigational product is classified as follows.

① Concomitant medication/combination therapy

② MRSA bacteremia

③ Underlying disease other than MRSA bacteremia

④ None

⑤ Unknown

⑥ Other

10.5.2.4. Treatment and Outcome

During the study period, the investigator must make every effort to ensure the safety of the subjects. In the event of a serious adverse drug reaction, the investigator must take immediate and appropriate action to minimize the adverse drug reaction and may suspend the study in consultation with the sponsor. All adverse events that occurred during the study period, even if not related to the investigational product, must be recorded in detail in the eCRF, including symptoms and signs, start/end date, duration, severity, treatment and outcome, causal relationship to the investigational product, seriousness, etc. In addition, adverse events shall be monitored for as long as possible until the condition or baseline prior to administration of the investigational product is restored, or until the investigator can determine that the adverse events have normalized, or until further observation is deemed unnecessary.

The criteria for the actions taken for the investigational product, the outcome of the adverse event, and the treatment of the adverse event are classified as follows.

1) Actions for the Investigational Product

① Drug withdrawn
② Dose reduced
③ Dose increased
④ Dose not changed
⑤ Unknown
⑥ Not applicable

2) Outcome of Adverse Event

① Recovered/resolved
② Recovering/resolving
③ Not recovered/not resolved/ongoing
④ Recovered/resolved with sequelae
⑤ Fatal
⑥ Unknown

3) Actions for Adverse Event

① Drug treatment
② Non-drug treatment
③ Drug and non-drug treatment
④ No treatment performed

10.5.2.1 Reporting of Adverse Events

The investigator will inform subjects (or their representatives) of any adverse events that may occur during the study period and instruct them to report any symptoms that occur during the study period. For adverse events that occur during the study period, the investigator shall record in the eCRF the type, start and end date, severity, treatment and outcome, and causal relationship to the investigational product. In addition, the adverse event should be followed up until its termination (disappearance of the adverse event, lost to follow-up, etc).

10.5.2.2 Expedited Reporting

The investigator must report all serious adverse events that occur during the study period to the sponsor (or the sponsor's designee) by e-mail or fax immediately or within one business day of becoming aware of them, regardless of their relationship to the investigational product. The investigator must also report to the IRB of each study site's within the specified reporting period.

If possible, all information on the serious adverse event form should be included in the initial report. The completed form should be sent to the sponsor and entered on the adverse event page of the eCRF.

Upon receipt of the initial report, the sponsor (or the sponsor's designee) and the IRB must review the information and request additional information from study personnel as appropriate. After reviewing the adverse event information, the causal relationship to the investigational product will be investigated.

If necessary, a follow-up report with any new information about the serious adverse event should be completed on the serious adverse event form and sent to the sponsor.

The sponsor must report serious and unexpected adverse drug reactions to the investigator, the Minister of Food and Drug Safety, and, if required, to the IRB within the following time limits.

- Death or life-threatening events: Within 7 days from the date the sponsor receives the report or becomes aware of the event. However, if not all information has been reported according to the adverse drug reaction report in the Annex Form No. 77, such as name of the adverse drug reaction, final observation result, summary of the adverse drug reaction, etc., an additional report with detailed information on the adverse drug reaction must be submitted within 15 days from the date on which the sponsor first received the report or became aware of the adverse drug reaction.
- For all other serious and unexpected adverse drug reactions, within 15 days from the date the sponsor receives the report or becomes aware of the case.

Contact information for reporting serious adverse events can be found in **Attachment 6**.

10.5.2.3 Duties of the Study Personnel in the Event of Serious Adverse Drug Reaction

During this study, the principal investigator and study personnel must make every effort to ensure the safety of the subjects and take immediate and appropriate measures to minimize adverse events. If a "serious adverse drug reaction" occurs during the study, each study personnel shall have the following duties.

1) Duties of the principal investigator

If a serious adverse drug reaction occurs during the study, the principal investigator must report it to the sponsor within 24 hours of becoming aware of it, or no later than the next working day, and to the IRB within the specified deadline so that a decision can be made as to whether the study should be continued or discontinued. In addition, the principal investigator must inform the subjects and take appropriate measures to minimize the adverse reaction.

2) Duties of the study personnel

If a serious adverse drug reaction occurs during the study, the study personnel must report it immediately to the principal investigator and the sponsor.

3) Duties of the Institutional Review Board

If a serious adverse drug reaction occurs during the study, the IRB must review the severity and causality of the adverse reaction and take the necessary measures, such as instructing the principal investigator to suspend all or part of the study.

4) Duties of the sponsor

If the sponsor receives a report of a serious and unexpected adverse drug reaction from the principal investigator or study personnel, the sponsor must include a summary of the adverse drug reaction, such as the adverse drug reaction report (Council for International Organizations of Medical Sciences form, CIOMS-I), submit it to the Minister of Food and Drug Safety, and immediately notify the institution of the case in accordance with the corresponding IRB regulations.

Serious adverse events will be followed and reported, including those that occur during the study period. The investigator will follow subjects until all serious adverse events have resolved or have been confirmed to persist in a semi-permanent state.

10.5.3 Follow-up of Adverse Events

Collected adverse events will be monitored until completion of the scheduled administration and all visit procedures. However, if new adverse events occur or if persistent adverse events are not resolved at the final visit, follow-up will continue until possible resolution has occurred or until the investigator determines that further follow-up is futile. The subject will be considered to have completed the study at the end of follow-up.

10.5.4 Pregnancy

Women of childbearing potential may only participate in this study if a pregnancy test confirms a negative result. Subjects must use adequate contraception during the study period and for 14 days after the end of the administration of the investigational product. Contraceptive methods allowed in this study are as follows.

* Contraceptive methods: Use of at least one barrier method (e.g., implants, injections, oral contraceptives, intrauterine devices (IUDs)) in combination with hormonal IUDs, absolute abstinence, or vasectomy (subjects must consent to the use of at least two contraceptive methods).

If pregnancy is confirmed during the study, this is not considered a serious adverse event or adverse drug reaction. However, the subject must be withdrawn from the study, and the progress of the pregnant woman and fetus should be followed and reported.

The investigator must complete and submit an initial pregnancy report to the sponsor (or the sponsor's designee) within 24 hours or by the next business day after becoming aware of the pregnancy. The investigator must track and document the progress and outcome of all pregnancies to the maximum extent possible, even if the subject withdraws consent or discontinues the study. In addition, the investigator must complete and submit a pregnancy follow-up report to the sponsor (or the sponsor's designee) within 24 hours or by the next business day of becoming aware of the pregnancy outcome. In addition, if consent is obtained, the newborn will be followed up until 28 days after birth.

10.6 PK Assessment

10.6.1 Assessment Methods for PK Parameters and MIC

1) PK parameters include C_{max}, AUC_{last}, T_{max} (hr), $T_{1/2}$ (hr), and CL and will be analyzed with samples collected at the time points specified in Section 10.1.13. PK analysis will be performed at a designated analysis institution according to a separate PK analysis plan.
2) 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. Evaluation of the MIC of LCB01-0371 will be performed at the time points specified in Section 10.1.11 when feasible, and the analysis will be performed separately at a designated analysis institution.

11 Data Analysis and Statistical Considerations

11.1 Analysis Sets

1) Safety Set (SS)

The SS will include all subjects who have received at least one dose of the study drug. For the safety analyses, subjects will be analyzed based on the treatment group to which they are actually administered.

2) Efficacy Analysis Set

The efficacy assessment will use the full analysis set (FAS) as the main analysis set, while the per protocol set (PPS) will be additionally analyzed as a subset.

FAS (Full analysis set)

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.

PPS (Per Protocol Set)

The PPS consists of subjects from the FAS who completed the study without any major protocol deviations.

Major protocol deviations include violation of the inclusion/exclusion criteria and administration of prohibited medications during the study period, treatment compliance < 80%, etc. Subjects with other major protocol deviations will be determined by case review (or blind data review).

11.2 Statistical Analysis Method

11.2.1 General Principles of Result Analysis

The efficacy evaluation analysis will be performed based on the “Full Analysis Set (FAS)” and the “Per Protocol Set (PPS)”, and the safety data will be analyzed using the Safety Set.

All statistical analyses will be performed using SAS® version 9.4 (or higher) and will be based on a two-sided test with a significance level of 5% when a significance test is required. If missing values occur at any time point, they will be treated as missing without imputation.

11.2.2 Demographic Data, Medical History, and Medication History

For subject demographic information (age, gender, etc.) and baseline characteristics in the safety set, continuous variables will be presented with descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum), and categorical variables will be presented with frequencies and percentages.

All collected medical history information will be standardized into SOC and PT using the latest version of MedDRA and frequencies, percentages, and number of cases by SOC and PT will be presented for the safety set.

All collected information on medication history will be standardized using the latest version of the Anatomical Therapeutic Chemical code (ATC code), and the number of subjects and the incidence and number of cases of

medication use will be presented based on the Anatomical Main Group (Level 1) and Therapeutic Subgroup (Level 2).

11.2.3 Analysis of Efficacy Endpoints

The efficacy evaluation analysis will be performed based on the "Full Analysis Set (FAS)" and the "Per Protocol Set (PPS)", and the FAS will be the primary analysis set. The time points for the assessment of the efficacy variables will be based on the time of blood collection for the blood cultures.

11.2.3.1. Primary Efficacy Endpoint

Proportion (%) of subjects with overall cure on Day 14 of treatment (composite response rate): 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)[a].

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

The number and percentage of subjects with overall cure within Day 14 of treatment will be presented with the corresponding two-sided 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.

11.2.3.2. Secondary Efficacy Endpoints

1) Proportion (%) of subjects with overall cure by the EOT visit (composite response rate)

   The number and percentage of subjects with overall cure by the EOT visit will be presented with the corresponding two-sided 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.

2) Mortality (%) due to MRSA bacteremia during the treatment period with the investigational product

   The number and percentage of subjects who died during the treatment period with 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.

3) Relapse rate of MRSA bacteremia: Proportion (%) of subjects with relapse MRSA bacteremia after two consecutive negative MRSA test results and prior to the TOC visit

   The number and percentage of subjects with relapse MRSA bacteremia after two consecutive negative MRSA test results and up 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.

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 on Day 3, Day 5, Day 7, Day 14 and at the EOT visit)

The number and percentage of subjects with clearance of MRSA bacteremia on Day 3, Day 5, Day 7, Day 14 and at the EOT visit will be presented with the corresponding two-sided 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.

5) Proportion (%) of subjects with persistent MRSA bacteremia based on blood culture results on Day 3, Day 5, Day 7, and Day 14.

The number and percentage of subjects with persistent MRSA-positive results in blood culture tests from the time of first MRSA positivity before randomization to each subsequent time point (Day 3, Day 5, Day 7, Day 14) will be presented with the corresponding two-sided 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.

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.

<Handling of the data for survival variables>

① Time to clearance of MRSA bacteremia

Status = 1 (event), if clearance of MRSA bacteremia

0 (censored), if no clearance of MRSA bacteremia

② Duration (days) = [(date of assessment of event/censored) – (date of first documented positive of MRSA before randomization) + 1]

The clearance of MRSA bacteremia is defined as an event, and the evaluation date is the date on which the first clearance of MRSA bacteremia is confirmed. In addition, subjects in whom MRSA bacteremia does not resolve and who are withdrawn from the study or lost to follow-up will be censored, and the evaluation date will be the date of withdrawal or the end of the study.

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). 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.

11.2.4 Analysis of Safety Endpoints

The efficacy analyses will be summarized and presented for the safety set.

1) Adverse events

The summary and analysis of adverse events will be performed for treatment-emergent adverse events (TEAEs). TEAEs are adverse events that were not present before administration of the investigational product but occurred after administration or adverse events that were present at baseline but worsened in severity after administration of the investigational product. The occurrence of treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) will be presented with the number and percentage (%) of subjects, number of occurrences, and the two-sided 95% confidence intervals for the percentages. In addition, AEs will be categorized and summarized as those related to the investigational product and those not related to the investigational product (such as concomitant medications and therapies, MRSA bacteremia, underlying diseases other than MRSA, none, unknown, or other related AEs). All TEAEs will be coded by SOC and PT based on the latest version of MedDRA, and their severity will be graded according to NCI-CTCAE v5.0. In addition, the number of subjects, incidence, number of cases will be presented for each code.

2) 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.

3) 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.

4) Abnormal changes in vital signs, electrocardiogram (ECG), laboratory tests, and physical examination

For continuous data such as vital signs, electrocardiogram, and laboratory tests (hematology and blood chemistry), descriptive statistics (number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for the measured value and the change from baseline at each visit. The results of laboratory tests and ECGs classified as normal, non-clinically significant (NCS) abnormal, or clinically significant (CS) abnormal will be summarized for subjects who exhibit CS abnormal results after treatment with the investigational product. Subjects who are classified as normal or NCS abnormal before administration of the investigational product but change to CS abnormal after administration of the investigational product will be listed separately. Subjects with abnormal CS findings on physical examination will also be listed.

11.2.5 Assessment of PK Parameters and MIC

1) PK assessment will be analyzed by a separate institution and summarized descriptively based on the data structure. The report on the results of the PK assessment can be presented separately from the clinical study report.
2) For MIC assessment, descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided for MIC measurements.

11.2.6 Subgroup Analysis

Subgroup analyses will be performed only for the following cases, and the detailed information will be described in the statistical analysis plan.

- Subjects who are switched to daptomycin treatment
- Subjects who are switched to oral antibiotics after treatment with vancomycin (including switching to daptomycin)
- Subjects who have received antiviral or antifungal medication during the study period

11.2.7 Safety Data Review Committee

The Safety Data Review Committee (SDRC), composed of members independent of the sponsor and investigator, will review blinded safety data by treatment group to assess causality with the investigational product and other factors, and the adverse event analysis will be conducted based on the causality assessment results by the SDRC. During the study, the SDRC will be convened as needed to review the safety data on a case-by-case basis, assess the causality of adverse events, and evaluate the benefits and risks of the treatment. The SDRC meetings will be held regularly, but the frequency will be appropriately adjusted according to the recruitment rate of subjects, collected data, etc. Other activities and responsibilities of the Safety Monitoring Committee are specified in the Charter of the Safety Data Review Committee (SDRC Charter).

11.3 Timing of Statistical Analysis

The final analysis of this study will be performed after the observation of all enrolled subjects is completed.

11.4 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.

12 Data Management

12.1 Records and Access

Source documents are defined as the results of the data collection activities and observations in the study. The source documents include medical records, electronic data, recorded measurements from instruments, etc., and may also include other records. All source documents available in this study will be recorded and retained by the investigator at the study institution, and only authorized personnel may access and review the source documents.

12.2 Data Collection

The Electronic Data Capture (EDC) system used in this study is in compliance with 21 Code of Federal Regulations (CFR) Part 11. The EDC system can only be accessed if authorized, and all traces of eCRF entered, modified, saved, or deleted through the EDC system will be recorded. The investigator shall guarantee that the data entered into the eCRF by electronic signature is accurate, complete, legible, and timely.

The eCRF generated through the EDC system will be delivered to each study site in an electronic storage medium upon completion of the study and retained according to the same standards as other trial master files.

12.3 Protection and Retention of Records

According to the relevant regulations for record retention in clinical studies, the principal investigator must retain various data (including electronic documents) related to the conduct of the study, such as the protocol and records of the manufacture and management of investigational products, etc., under appropriate retention conditions for at least 3 years from the date of completion of the study (or from the date of product approval). However, the retention period may be extended if deemed necessary by the sponsor.

These documents will be examined in case of an inspection by the sponsor or related regulatory authorities, and the investigator may not destroy any documents related to the study without written authorization from the sponsor. The investigator should take precautions to prevent inadvertent or premature destruction of these documents.

12.4 Data Safety Monitoring Plan

The principal investigator must protect the subject's information by managing the documents related to this study so that they cannot be disclosed. To ensure the completeness of the study data, the principal investigator will periodically check to see if the storage location of the source documents has changed and if unauthorized persons have accessed them. In addition, the principal investigator must verify that the study is proceeding according to the objectives of the protocol (adequacy of subject recruitment, safety and efficacy assessments in accordance with the protocol, proper reporting/recording of adverse events, etc.), protect subject safety, and ensure completeness of data by preparing case report forms based on the source documents.

In addition, the monitor must report the safety data confirmed by this monitoring process to the investigator, who is in a position to make a medical judgment, and the investigator makes the final decision on recommendations resulting from this data safety monitoring:

- Recommendations to continue or discontinue the study
- Recommendations on subject recruitment/selection/retention and management, improving adherence to the protocol, and data management and quality control procedures to ensure the integrity of the study
- Evaluation of information on risks that exceed the benefits of the investigational product or on adverse events, suboptimal effects for recommendation of methods to reduce risks such as adverse events
- Review data completeness etc., by obtaining monitoring results related to protocol deviations and study withdrawals as they occur

13 Ethics Considerations and Administrative Procedures

13.1 Compliance with Regulations and Ethics (KGCP)

This study will be conducted ethically and scientifically in accordance with the Korean Good Clinical Practice (KGCP) and all relevant regulations. In addition, based on the Helsinki Declaration, the study will respect human dignity and rights and will not cause any disadvantage to the subjects.

13.2 Institutional Review Board (IRB)

Prior to the start of the study, the investigator must obtain written approval from the IRB for the study protocol, informed consent form, subject recruitment materials and procedures, and subject information sheets.

The IRB of each study site shall review the ethical, scientific, and medical validity of the study and communicates its decisions in writing to the principal investigator and the sponsor prior to the start of the study.

The principal investigator will report to the IRB on the progress of the study and any SAEs, life-threatening issues, or deaths and must inform the IRB at the end of the study.

13.3 Informed Consent Process

In conducting this study, the investigator must obtain written informed consent from the subject (or the subject's representative) after adequately informing the subject of the content and procedures of the study, the effects of the investigational product, and the possible adverse events. The written informed consent must be obtained prior to all other study procedures. The investigator must provide the subject (or the subject's representative) with a copy of the signed informed consent form and a copy of the subject information sheet, and the original must be retained in the investigator's file.

See **Attachment 4. Subject Information Sheet and Informed Consent Form**.

The principal investigator or study personnel must never coerce participation or exert undue influence, and the informed consent form and study-related information (including both verbal and written information) must not contain any content that restricts or could restrict the rights of the subject or the subject's representative, or any content that relieves or could relieve the investigator, study site, sponsor, or sponsor's representative from responsibility.

In addition, simple terms that can be understood by the subject, the subject's representative, or witnesses must be used.

Prior to obtaining informed consent from the subject, the principal investigator or his/her designee shall give the subject or his/her representative sufficient time and opportunity to ask questions about the details of the study and to decide whether the subject wishes to participate in the study, and will honestly answer any questions the subject or his/her representative may have about the study.

If the subject or the subject's representative is unable to read the informed consent form, the subject information sheet or other documented information, a witness must be present throughout the informed consent process. In this case, the principal investigator or his/her designee must read and explain the consent form, subject information sheet, and other documented information to the subject or his/her representative, and the subject or his/her representative must verbally consent to participate in the study and, if possible, personally sign and date the consent form. The witness must personally sign and date the consent form. Before signing the consent form, the witness must confirm the following:

- Whether the consent form, subject information sheet, and other documented information were accurately explained to the subject or the subject's representative
- Whether the subject or the subject's representative understood the information
- Whether the consent process was conducted according to the free will of the subject or the subject's representative

By signing the informed consent form, the subjects agree to participate in the study and to the collection and use of their personal information in connection with the study. The personal information collected in connection with the study will include personal identification data (name, contact information, etc.), demographic data, medical records (medical history, treatment history, etc.), and test results performed in connection with the study. All data collected will be handled in accordance with the laws, rules, and regulations on the protection of personal data.

13.4 Measures to Protect the Safety of Subjects

The IRB shall evaluate/approve this protocol in accordance with Good Clinical Practice (GCP) and will periodically review the protocol compliance of the study. The study personnel and participating investigator will thoroughly analyze and familiarize themselves with the protocol. The principal investigator will take preparatory measures, such as sufficient preparation for unexpected adverse events, necessary reporting, adequate training of the investigator, and conduct of the study according to GCP standards.

13.4.1 Measures in the Event of Adverse Events

If adverse events occur due to this study despite the investigator conducting the study in strict compliance with all relevant laws and regulations and following the protocol and various related literature, recommendations, and suggestions of the sponsor, the investigator must immediately initiate the necessary examinations and treatment. In addition, if necessary, observation should be performed until the adverse event resolves or the subject is lost to follow-up.

13.4.2 Treatment and Care of Subjects after the Study

Subjects who are withdrawn from the study can receive other appropriate treatment. Subjects who have completed the study will receive the most appropriate treatment as determined by the investigator.

13.4.3 Compensation Rules

In the event of harm caused by the investigational product, the sponsor will compensate the subject in accordance with the compensation rules for injured subjects.

See **Attachment 2. Subject Compensation Rule**.

13.5 Publication of Study Results and Confidentiality of Subject Records

All records that can identify the subject must be kept confidential. All documents related to the study, such as case report forms, will be recorded and classified using the subject identification code and not the subject's name. The identity of the subjects will be kept confidential, even if the results of the study are published.

The sponsor or monitors and inspectors, as well as the Ministry of Food and Drug Safety and the IRB, may access the subjects' medical records to verify the information collected. However, subject information must be kept strictly confidential even during such reviews.

The sponsor will fully analyze the data received from all study sites and inform the investigator of the results of the study by preparing a clinical study report.

13.6 Quality Control and Reliability Assurance

13.6.1 Study Site Monitoring

Monitoring of the study will be conducted to protect the rights and welfare of the subjects and to ensure that the data reported in the study are accurate, complete, and verifiable against the source documents and that the study is conducted in compliance with the approved protocol, the KGCP, and relevant regulations. The study will be monitored through regular visits and contacts with the study site by the sponsor (the sponsor's designee) or a monitor. These visit schedules should be appropriately discussed and distributed between the investigator and the monitor. Basically, the monitor must review the source documents, management records of the investigational product, document retention status, etc., and examine the overall progress of the study. In addition, any issues found must be discussed with the investigator, and the investigator must cooperate in this process.

13.6.2 Audit

The sponsor may conduct audits during or after the study to ensure the reliability of the study. The audit will include checking whether this study is conducted in compliance with the relevant regulations such as the protocol, standard operating procedures, KGCP, etc., and review of all source data, drug history, medical history, etc. The sponsor (the sponsor's designee) may request access to the source documents and other trial master files for the audit of the study site, and the investigator must allow it and cooperate in this process.

13.6.3 Inspection

The Ministry of Food and Drug Safety may conduct inspections during or after the study. If inspections are scheduled, the investigator must inform the sponsor immediately. The Ministry of Food and Drug Safety may

request access to source documents and other trial master files for the inspection of the study site, and the investigator must allow it and cooperate with this process.

14 Sponsor Information and Name and Title of the Principal Investigator

14.1 Sponsor Information

Sponsor: LegoChem Biosciences, Inc.

CEO: Yong Joo Kim

Address: 8-26, Munpyeongseo-ro, Daedeok-gu, Daejeon, Republic of Korea

14.2 Name and Title of the Principal Investigator

See Attachment 3. List of Study Sites and Investigators for the names and positions of the principal investigator of each study site.

15 Other Requirements for Safe and Scientific Conduct of the Study

15.1 Protocol Amendment

If the approval of the study is to be obtained or if the approved study has been modified, IRB approval must be obtained for the amended study protocol and, if required, approval must also be obtained from the Minister of Food and Drug Safety.

16 References

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17 Appendices

Appendix 1 Precautions for Use of Vancomycin

1. Do not administer to the following patients:
   1) Patients with a history of shock to vancomycin
   2) Patients with a history of hypersensitivity to vancomycin, peptide antibiotics, or aminoglycosides
2. Vancomycin should be administered carefully to the following patients:
   1) In principle, vancomycin should not be administered to patients with hearing loss or hearing loss caused by peptide antibiotics and aminoglycoside antibiotics. However, if administration is unavoidable, it should be done with caution.
   2) Patients with renal impairment such as acute urinary retention (administer with caution while monitoring blood concentrations as excretion is delayed and accumulation occurs).
   3) Patients with hepatic impairment (vancomycin may cause or exacerbate hepatic impairment).
   4) Elderly
   5) Premature infants, neonates
   6) Patients with vestibular and cochlear damage
3. Adverse events
   1) Psychiatric and nervous system: Shock and anaphylactoid reactions may occur in rare cases. Therefore, observe carefully and discontinue administration and take appropriate action if adverse reactions occur.
   2) Digestive system: Rarely, red stools, diarrhea, nausea, vomiting, and abdominal pain may occur.
   3) Blood system: Occasionally, decreased red blood cells, decreased white blood cells, decreased platelets, and increased eosinophils may occur. Reversible neutropenia has been reported, which recovered immediately after discontinuation of the drug. In addition, reversible agranulocytosis (granulocyte count $\leq 500/mm^3$) has been reported in rare cases, although causality has not been established.
   4) Central nervous system: Disorders of the 8th cranial nerve such as dizziness, tinnitus, and reduced hearing may occur rarely. Therefore, monitor the patient carefully including conducting hearing tests. If these symptoms occur, it is generally recommended to discontinue the administration, but caution is advised if administration must continue. Hearing loss has been reported in patients with renal impairment, a history of hearing loss, or concomitant administration of other ototoxic drugs in conjunction with vancomycin.
   5) Liver: Elevated bilirubin, AST, ALT, and ALP, and rarely elevated LDH, γ-GTP, and LAP may occur. Therefore, conduct regular tests, observe carefully and discontinue the administration or take appropriate action if adverse reactions occur.
   6) Kidney: Renal failure, including elevated BUN and creatinine may occur. Therefore, perform regular tests and observe the patient carefully. If adverse reactions occur, it is generally recommended to discontinue the administration, but caution is advised if administration must continue. In addition, interstitial nephritis has been reported rarely in patients receiving concomitant aminoglycoside antibiotics and in patients with a history of renal impairment. Azotemia was resolved upon discontinuation of vancomycin treatment.

7) Skin: Exfoliative dermatitis, bullous dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis may occur.

8) Hypersensitivity: Rash, erythema, facial flushing, hypotension, wheezing, dyspnea, urticaria, and pruritus may occur; if these symptoms occur, take appropriate action. In addition, a rapid infusion can also cause red man syndrome (erythematous flushing of the skin on the neck, shoulders, and upper body) or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals receiving a rapid, high-dose intravenous infusion. Such reactions are infrequent if vancomycin is given by a slow infusion over 60 minutes. In studies of healthy volunteers, infusion-related reactions did not occur when vancomycin was administered at a rate of 10 mg/min or less.

9) Other: Occasionally fever, vascular access pain, and phlebitis may occur, and rarely nausea, chills, and vasculitis may occur. In addition, pseudomembranous colitis caused by Clostridium difficile has been rarely reported in patients receiving vancomycin intravenously.

10) Based on the analysis and evaluation of adverse reaction reports in Korea, the following adverse reactions are added.
- Skin: Maculopapular rash, purpura (purpuric rash), vesicular rash
- Hepatobiliary system: Jaundice
- Injection site: Rash

11) Based on the analysis of the data from the post-marketing adverse reaction reports (December 1989-December 2018), the following new adverse reactions were identified.
- Genitourinary system - Renal tubular necrosis (acute tubular necrosis)

4. Drug interactions

1) Concomitant administration of vancomycin and anesthetic agents has been associated with increased anaphylactoid reactions, including erythema, histamine-like flushing, hypotension, wheezing, dyspnea, urticaria, or pruritus. These reactions can be lessened by infusing vancomycin over at least 60 minutes before anesthetic induction.

2) Caution should be exercised in patients receiving vancomycin and concurrent and/or sequential systemic or topical use of other potentially, neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, or platinum-containing anticancer drugs (cisplatin, nedaplatin, etc.) as it can enhance the adverse reactions.

3) International Normalized Ratio (INR) changes: Increased anticoagulant activity has been reported in patients receiving antibiotics, including vancomycin, concomitantly with anticoagulants. Infectious diseases (and associated with inflammatory processes), the patient's age and general condition are risk factors. Although the interaction between vancomycin and warfarin has not been established through clinical studies, the INR monitoring should be conducted and the dosage of the oral anticoagulant adjusted accordingly if necessary. This is more severe with certain types of antibiotics, particularly fluoroquinolones, macrolides, cyclines, cotrimoxazole, and some cephalosporins.

5. Management of overdose
    1) Symptoms: Renal disorders such as acute renal failure and 8th cranial nerve disorders such as hearing loss may occur.
    2) Treatment: Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance. The mean lethal intravenous dose is 319 mg/kg in rats and 400 mg/kg in mice.
6. Precautions for storage and handling
    1) Vancomycin is irritating to tissue and must be given by a secure IV route of administration. Pain, tenderness, necrosis, etc., may occur with intramuscular (IM) injection of vancomycin or with inadvertent extravasation.
    2) IV injection of high concentrations may cause thrombophlebitis. The frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5-5 g/L) and by rotation of venous access sites.
    3) Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension, including shock and rarely cardiac arrest. Therefore, vancomycin should be administered over a period of not less than 60 minutes to avoid infusion-related reactions. Stopping the infusion usually results in prompt cessation of these reactions.
    4) The safety and efficacy of administering vancomycin by the intrathecal (intralumbar or intraventricular) route have not been assessed.
    5) Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds. Vancomycin should not be mixed with alkaline solutions.
    6) Mixtures of solutions of vancomycin and beta-lactam antibacterial drugs have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush the intravenous lines between the administration of these antibacterial drugs. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less.
    7) Although intravitreal injection is not an approved route of administration for vancomycin, precipitation has been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles. The precipitates dissolved gradually, with complete clearing of the vitreous cavity over two months and with improvement of visual acuity.
    8) The drug product should be visually inspected for particulate matter and discoloration prior to administration via injection.

Appendix 2 Precautions for Use of the Study Drug

The following adverse drug reactions were reported in six Phase 1 clinical studies of LCB01-0371 in healthy adult male volunteers and in one Phase 2a clinical study of LCB01-0371 in tuberculosis patients.

Comprehensive Adverse Event and Potential Risk List (17 Jun 2022)

Adverse Event	Severity
Ear and labyrinth disorders	
Ear swelling	Mild
Eye disorders	
Hordeolum left	Mild
Ocular hyperaemia	Mild
Visual impairment	Mild
Gastrointestinal disorders	
Abdominal discomfort	Mild
Abdominal distension	Mild
Abdominal pain	Mild
Constipation	Mild
Diarrhoea	Severe
Dyspepsia	Moderate
Gastric discomfort	Mild
Nausea	Moderate
Pangastritis	Severe
Vomiting	Moderate
General disorders and administration site conditions	
Asthenia	Mild
Feeling cold	Mild
Fever	Mild
Infusion site pain, Right arm	Mild
Infusion site paraesthesia, right lower arm	Mild
Infusion site phlebitis left arm	Mild
Left sided chest pain	Mild
Malaise	Mild
Vessel puncture site erythema, right	Mild
Injury, poisoning and procedural complications	
Laceration, right eyebrow	Mild
Laceration, 2nd right finger	Mild
Forearm bruise, left	Mild
Infections and infestations	
Periumbilical abscess	Moderate
Tuberculosis	Death
Investigations	
Hematology test abnormal	Mild
Liver function test abnormal	Moderate
ALT increased	Mild
AST increased	Mild
Bilirubin total increased	Mild
Blood bilirubin increased	Mild

Blood creatine phosphokinase increased	Severe
Creatine kinase increased	Mild
Neutrophil count decreased	Severe
Platelet count decreased	Mild
White blood cell count decreased	Moderate
White blood cells urine positive	Mild
Metabolism and nutrition disorders	
Decreased appetite	Mild
Gout	Moderate
Hypertriglyceridemia	Mild
Hyperuricemia	Mild
Hypoglycemia	Mild
Malnutrition	Mild
Musculoskeletal and connective tissue disorders	
Arthralgia	Moderate
Acne, forehead	Mild
Back pain	Mild
Musculoskeletal pain	Mild
Swelling of the right knee	Mild
Myalgia	Mild
Pain in extremity	Mild
Nervous system disorders	
Dizziness	Moderate
Headache	Moderate
Migraine	Mild
Tingling sense, left leg	Mild
Paraesthesia	Mild
Psychiatric disorders	
Sleep disorder	Mild
Insomnia	Mild
Renal and urinary disorders	
Urinary hesitation	Moderate
Respiratory, thoracic and mediastinal disorders	
Cough	Mild
Dyspnea	Moderate
Hemoptysis	Mild
Nasal stuffiness	Mild
Sore throat	Mild
Non-cardiac chest pain	Mild
Oropharyngeal pain	Mild
Pneumothorax	Mild
Rhinorrhea	Mild
Somnolence	Mild
Tracheal stenosis	Moderate
Skin and subcutaneous tissue disorders	
Acne	Mild
Eczema	Mild
Pruritus	Mild

Rash	Mild
Rash maculo-papular	Mild
Skin eruption, neck and trunk	Mild
Sweating	Moderate
Urticaria	Mild
Vascular disorders	
Distributive shock	Moderate

Appendix 3 Precautions for Use of Daptomycin

1. Do not administer to the following patients:
   1) Patients history with hypersensitivity to daptomycin or any of its other components.
2. Daptomycin should be administered carefully to the following patients:
   1) Patients with persisting or relapsing *S. aureus* bacteremia/endocarditis.
   2) Patients with moderate to severe renal impairment.
   3) Patients with symptoms or signs of peripheral neuropathy.
   4) Patients receiving warfarin.
3. Adverse events
   1) Blood/lymphatic system: Eosinophilia, lymphadenopathy, thrombocythemia, thrombocytopenia
   2) Cardiovascular system: Atrial flutter, cardiac arrest
   3) Ear and labyrinth system: Tinnitus
   4) Ophthalmic system: Blurred vision
   5) Gastrointestinal system: Upper abdominal discomfort, gingival pain, oral hypesthesia
   6) Infections and infestations: Candida infection, vaginal candidiasis, fungemia, oral candidiasis, urinary tract fungal infection
   7) Investigations: Phosphorus increased, ALP increased, INR increased, abnormal liver function test, ALT increased, AST increased, prolonged prothrombin time
   8) Metabolism and nutritional system: Decreased appetite
   9) Musculoskeletal system: Myalgia
   10) Nervous system: Dyskinesia, paresthesia
   11) Psychiatric system: Hallucination
   12) Renal/urinary system: Proteinuria, renal failure
   13) Skin and subcutaneous tissue system: Miliaria, generalized pruritus, vesicular rash
4. Drug interactions
   1) Tobramycin: In a study in which 6 healthy adult males received a single dose of daptomycin 2 mg/kg IV, tobramycin 1 mg/kg IV, and both in combination, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin were 12.7% and 8.7% higher, respectively, when daptomycin was co-administered with tobramycin. Similarly, the mean C_{max} and $AUC_{0-\infty}$ of tobramycin were 10.7% and 6.6% lower, respectively, when tobramycin was co-administered with daptomycin. However, these differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose (4 mg/kg) of daptomycin is unknown. Caution should be exercised when daptomycin is administered concomitantly with tobramycin.
   2) Warfarin: In 16 healthy adult subjects, administration of daptomycin 6 mg/kg every 24 hours by IV infusion over 30 minutes for 5 days, with co-administration of a single oral dose of warfarin (25 mg), had no significant effect on the pharmacokinetics of either drug and did not significantly alter the international normalized ratio (INR).

3) Simvastatin: In subjects on a stable daily dose of simvastatin 40 mg, administration of daptomycin 4 mg/kg IV for at least 30 minutes every 24 hours for 14 days (n=10) had no effect on plasma concentrations of simvastatin and was not associated with a higher incidence of adverse events, including skeletal myopathy, than in subjects receiving placebo once daily (n=10).

4) Probenecid: Concomitant administration of probenecid (500 mg 4 times daily) and a single dose of daptomycin 4 mg/kg IV did not significantly alter the C_{max} or $AUC_{0-\infty}$ of daptomycin. No dose adjustment is required for the concomitant administration of probenecid and daptomycin.

5. Management of overdose

Supportive care is required for the maintenance of glomerular filtration in case of overdose with daptomycin. Approximately 15% of daptomycin is cleared slowly from the body by hemodialysis over 4 hours, and approximately 11% of daptomycin is cleared by peritoneal dialysis over 48 hours. Use of high-flux dialysis membrane hemodialysis for 4 hours may increase the percentage of dose removal compared to the low-flux membrane.

6. Precautions for storage and handling

1) This drug is supplied as a sterile lyophilized powder in a single-use vial containing 500 mg or 350 mg of daptomycin. Before use, daptomycin should be reconstituted with 0.9% sodium chloride injection to a concentration of 50 mg/mL.

① To minimize foaming, avoid vigorous agitation or shaking of the vial during or after reconstitution.

② Remove the polypropylene flip-off cap from the glass vial to expose the central portion of the rubber stopper.

③ Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.

④ Slowly transfer 10 mL (7 mL for 350 mg) of 0.9% sodium chloride injection through the center of the rubber stopper into the daptomycin for injection vial, pointing the transfer needle toward the wall of the vial. It is recommended that a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device is used, pointing the transfer needle toward the wall of the vial.

⑤ Ensure that all of the daptomycin for injection powder is wetted by gently rotating the vial.

A. Allow the wetted product to stand undisturbed for 10 minutes.

B. Gently rotate or swirl the vial contents, as needed, to obtain a completely reconstituted solution.

2) The drug product should be inspected visually for particulate matter prior to administration.

3) The reconstituted daptomycin should be further diluted with 0.9% sodium chloride injection and administered IV for more than 30 minutes.

4) No preservative or bacteriostatic agent is included in this product. Aseptic technique must be used in the preparation of final IV solution.

5) Stability studies have shown that the reconstituted solution is physically and chemically stable for 12 hours at 25℃ and up to 48 hours at 2-8℃. The diluted solution is stable in the infusion bag for 12 hours at 25℃ and up to 24 hours at 2-8℃.

6) Since only limited data are available on the compatibility of daptomycin with other IV substances, additives and other medications should not be added to daptomycin single-use vials or infusion bags, or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of different drugs, the line should be flushed with a compatible intravenous solution before and after infusion with daptomycin.
7) Compatible infusion solutions: 0.9% Sodium chloride injection and lactated Ringer's injection.
8) Daptomycin is not compatible with dextrose-containing diluents.
9) Daptomycin should not be used in conjunction with ReadyMED® elastomeric infusion pumps.

18 Attachments

Attachment 1. Protocol Agreement
Attachment 2. Subject Compensation Rule
Attachment 3. List of Study Sites and Investigators
Attachment 4. Subject Information Sheet and Informed Consent Form
Attachment 5. Information Sheet and Informed Consent Form for Use of Pregnancy Information
Attachment 6. Contact Information for Serious Adverse Event Reporting