A randomized, double-blind, placebo-controlled, multicenter phase IIa clinical study to evaluate safety and to explore efficacy of N-Rephasin® SAL200 in patients with persistent Staphylococcus aureus bacteremia

ClinicalTrials.gov ID: NCT03089697

Statistical Analysis Plan

A randomized, double-blind, placebo-controlled, multicenter phase IIa clinical study to evaluate safety and to explore efficacy of N-Rephasin® SAL200 in patients with persistent *Staphylococcus aureus* bacteremia

Final Version

Date: December 06, 2019

DocuSign Envelope ID: EF728426-35FD-4879-85B1-3DE547615E86

SAP APPROVAL

※ Signatures

	Name/Position	Signature	Date (DDMMMYYYY)
Prepared by	Sunyoung Lee / Biostatistics Manager, Symyoo		06 DEC 2019
Reviewed by	DongJin Yoo / Medical Writer, Symyoo		06 Dec 2019
Approved by	Sunyoung Lee / Biostatistics Manager		06 DEC 2019
Approved by	Sooyoun Jun / Project Manager, iNtRON biotechnology		17 DEC 2019
Approved by	Steven Shen, PhD./ Head of Statistics, Roivant Pharma		17 Dec 2019
Approved by	Arnaud Bastien, MD/ Head of Clinical Development, Roivant Pharma	Arnaud Bastien	12/19/2019
Approved by	David Moore/ CEO, Lysovant		12/19/2019

SAP REVISION HISTORY

Version	Date(DDMMMYYYY)	Author	Reason for revision
1.1	DDNOV2019	Sunyoung Lee	Amended of typo or translation error: 2.3 sample size rationale. Additional written a paragraph or sentences to clarify the meaning: 2.5 progressive schedule of the study Efficacy endpoint and analysis method related background medication have added on 3.2.3 and 3.4.5 sections. Analyses for both safety and efficacy are repeated at the EOT visit, as long as the data at EOT are available.

Table of Contents

Abbreviations and definitions

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CPK	Creatine Phosphokinase
CRF	Case Report Form
ECG	Electrocardiogram
(K)GCP	(Korea) Good Clinical Practice
HED	Human Equivalent Dose
IBW	Ideal Body Weight
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MRSD	Maximum Recommended Starting Dose
NAS	Network-Attached Storage
NCE	New Chemical Entity
NOAEL	No Observed Adverse Effect Level
PK	Pharmacokinetic(s)
PT	Prothrombin time
RBC	Red Blood Cell
SBP	Systolic Blood Pressure
t_{max}	Highest concentration after single dose (C_{max})
WBC	White Blood Cell
MSSA	Methicillin Sensitive *Staphylococcus aureus*
MRSA	Methicillin Resistant *Staphylococcus aureus*

1 Introduction

This statistical analysis plan (SAP) contains a comprehensive and detailed description of the statistical procedures and techniques such as the definitions of analysis populations, derived variables, imputation rules for missing values and statistical methods for the protocol, ITB-101(version 2.1, effective date: 2019. 05. 09), which aims to evaluate the safety and efficacy of N-Rephasin®SAL200 in patients with persistent *Staphylococcus aureus* bacteremia.

2 Study Objectives and Design

2.1 Study Objectives

A phase IIa clinical study will be conducted to evaluate safety and efficacy of intravenous N- Rephasin® SAL200 (3 mg/kg) in addition to conventional standard therapy for persistent *S.aureus* bacteremia, on patients with *S. aureus* bacteremia that persist for more than 48 hours despite antibiotic theraphy that is sensitive to *Staphylococcus aureus*.

2.2 Study Design

A randomized, double-blind, placebo-controlled, multicenter phase IIa clinical study to evaluate safety and to explore efficacy of N-Rephasin® SAL200 in patients with persistent *Staphylococcus aureus* bacteremia

2.3 Sample Size and Rationale

This study is a phase 2 clinical study evaluating clinical efficacy and safety when N-Rephasin® SAL200 is administered to patients with persistent bacteremia caused by *S. aureus*, in addition to the existing standard treatment regimen.

The primary endpoints are safety endpoints. The distribution of the number of subjects who have experienced at least one side effect (incidence), and the distribution table for the study drug association (severity and drug association distribution table) for the reported adverse events are presented and evaluated by groups (active group, control group). The aim of this study is to obtain basic data on study and control drugs.

The primary evaluation will use descriptive statistics for the study drug and the control drug, hypothesis testing will not be performed. Considering the representativeness of the active group and the control group, the number of subjects required was 20, and each group was divided into 25 subjects considering the discontinuation rate of 20%.

Arms	Drug Regimen	Safety Evaluation No. of subjects	Number of subjects reflecting the drop out rate of about 20%
Control Group	MSSA/MRSA Standard Medication + Placebo	20	25
Treatment Group	N-Rephasin® SAL200, in addition to existing standard MSSA/MRSA medication	20	25

The total of 50 subjects will be divided into two Stages, Stage 1 (28 to 32 patients) and Stage 2 (about 22 patients). Upon the completion of stage 1 of the clinical study, at the discretion of the sponsor, IDMC(Independent Data Monitoring Committee) will evaluate the safety and efficacy of the drug and enter stage 2 if the drug is safe.

Number of subjects per stages

Stage 1	Interim Evaluation	Stage 2
28~32 subjects		About 22 subjects

As the early phase P2a study, the sample size is evaluated and decided without the justifications for demonstrating the treatment difference. The results from any analyses of the study will be reviewed for information, not for conclusions of the treatment comparisons.

According to early termination of the management decision, statistical analysis will be performed after quality control of collected data so far through the data management; 27 subject were enrolled and 25 subjects dosed the study according to check of subject status.

2.4 Inclusion and Exclusion Criteria

■ Inclusion Criteria

In the clinical study, candidates who meet the following conditions are selected.

1) Inclusion Persons with persistent MSSA/MRSA bacteremia with two or more positive pairs of blood cultures for gram-positive bacteria in cocci blood cultures performed at 48~96 hours from the start of antibiotic treatment susceptible to *S.aureus*;
2) Men and women aged 19 and over;
3) Persons who understand the content of the subject's information sheet and have signed and submitted the written consent.

■ Exclusion Criteria

Patients with any of the following conditions cannot participate in this study.

1) If the appropriate antibiotic is not administered within 48 hours after the occurrence of bacteremia (at the time of diagnosis);
2) If the mycetoma of gram-positive bacteria identified in blood cultures performed at 48 ~ 96 hours from the start of antibiotic treatment susceptible to *S.aureus* is not identical to that of *S.aureus* cultured at the point of definite diagnosis of *S.aureus* bacteremia;
3) Persons with persistent *S.aureus* bacteremia confirmed more than 48 hours ago, through blood cultures performed at 48 ~ 96 hours from the start of antibiotic treatment susceptible to *S.aureus*
4) Persons with septic shock at the time of obtaining written consent;
   - Persons with, despite adequate fluid therapy, systolic blood pressure less than 90 mmHg or 40 mmHg below normal blood pressure;
   - Persons with a need for a booster to maintain the systolic blood pressure above 90 mmHg;
5) Persons infected with mixed bacteria;
6) Persons with hypersensitivity or clinically significant hypersensitivity to N-Rephasin® SAL200 or history thereof;
7) Pregnant or lactating women and fertile women (Persons who are likely to become pregnant without proper contraception during the study);
8) Persons who participated in other clinical studies within 30 days from the registration date;
9) Patients of any condition that the Investigator judges will interfere with the study participation or the correct evaluation.
10) Persons who are judged by the researcher to die within 72 hours due to other serious complications (e.g. cerebral infarction)

2.5 Progressive Schedule of the Study

Progressive Schedule of the Study Observational items		Screening[10]	Treatment				Follow-up[11]
		D-1	D1[12]	D2	D3 -D13	D14	4W ± 5d
Written Consent		√					
Confirm Selection/Exclusion Criteria		√					
Random Assignment			√				
Disease History		√					
Demographic Data		√					
Vital Signs		√	√[2]	√	√	√	(√)
Physical Examination		√		√	√[3]	√	(√)
Experiment Results Examination	Blood Test	√		√	√[4]	√	(√)
	Blood Chemistry Test	√		√	√[4]	√	(√)
	Urinalysis	√		√	√[4]	√	(√)
Anaphylaxis Test			√	√	√[5]		
Inflammatory Cytokine Test			√	√	√[5]		
Pregnancy Test		√					(√)
Skin Reaction Test		√					
Investigational Product dosing			√				
Essential Concomitant Medication Administration			√	√	√	√	
Blood Culture/Evaluation (blood sampling)				√	√[9]	√	
Check for Concomitant Medication Use		√	√	√	√	√	√
Check for Concomitant treatment			√	√	√	√	√
Adverse Event			√	√	√	√	√

1. Subjects who have passed the screening will be given the subject number through random assignment.
2. The vital signs are measured once daily (including screening) for the rest of the treatment period excluding Day 1, and for Day 1, 12 measurements will be taken in the following timetable.

- Before Investigational Product dosing (1 time)
- 15 minutes, 30 minutes after study drug dosing (2 times)
- Immediately, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 8 hours, 16 hours, 24 hours after termination of Investigational Product dosing (9 times)

3. Physical examination is performed on screening, Day 2, and from Day 2 onward, at <2 days, 1 time> intervals, and blood cultures/evaluations are performed continuously until the second consecutive negative (successful treatment).
4. Experiment result examination should be conducted on Screening, Day 2, and Day 7 (± 48 hours) and Day 14 (± 48 hours) after Day 2.

Hematological test	WBC, RBC, Hemoglobin, Platelets
Blood biochemical test	Total protein, Albumin, Total bilirubin, AST, ALT, ALP, Total cholesterol, Serum creatinine
Urine test	Protein, Glucose, Blood, Ketones

5. Anaphylactic and inflammatory cytokine tests are performed on Day 1 (Immediately before the dosing of the study drug and after the dosing of the study drug), Day 2, and Day 7 (± 48 hours).

Anaphylactic test	C3a, C4a, Mast Cell Tryptase
Inflammatory cytokine test	IL-1b, IL-2, IL-6, TNF-α

6. Urine hCG should only be used for fertile women.
7. Registered subjects will receive the Investigational Product on Day 1.
8. Essential concomitant medication dosing shall only be from the drugs listed in '11.7.1 Essential concomitant

medications,' under the judgment of the researcher.

9. Day 2 blood sample collection for blood cultures should be performed within 18 hours (± 6 hours) of the dosing of the study drug. Day 3 to Day 8 blood culture sampling should be performed 24 hours (± 6 hours) from the collection of previous blood samples for blood culture (1 time/Day). Blood samples for blood cultures from Day 8 to Day 14 should be collected from blood samples collected 48 hours (± 6 hours) from the previous blood culture samples (1 time/2Day). During the entire study period, blood samples for blood cultures should be collected consecutively until the second consecutive negative (successful treatment) from blood culture.
10. In the screening, the study record can be used without any further examination, if there is a record of the subject for that item 7 days before the screening..
11. At 4W ± 5days follow-up, examine the date on the subject's visit and check the concomitant medication and adverse event by telephone visit. The subjects who can visit the outpatient clinic will be checked for concomitant medication and adverse events as well as signs of vital signs, physical examinations and laboratory tests.
12. Day -1 and Day 1 schedules can be conducted simultaneously for the subjects fulfilling the inclusion criteria.
13. Day 7 If two consecutive days in the previous year are negative (treatment completed), additional laboratory tests, anaphylaxis tests and inflammatory cytokines should be performed

3 Statistical Methods

3.1 Analysis Populations

The data obtained from the subjects of this study are largely analyzed in two sets:

- Safety set :
  All patients who were enrolled, randomized in the study and received at least one study drug/control drug.

- Full Analysis set(FA set):
  All patients who were enrolled, randomized in the study and received at least one study drug/control drug and who have had bacteremia(blood culture) test results at least once.

3.2 Study Endpoints

3.2.1 Primary analysis (Safety analysis)

The following safety endpoints will be collected through the eCRF.

1) Treatment emergent Adverse event (TEAE)

A treatment emergent adverse event is any undesirable and unintended sign that occurs or worsens in a patient starting the of receiving the Investigational product or a subject during the observation period of the study. This does not necessarily have to have a causal relationship with the drugs. That is, those that are not correlated with Investigational Product or the study are also included in the use of the term “adverse event”. Clinically significant abnormal results of diagnostic procedures, including abnormal laboratory findings (e.g. unplanned diagnostic procedures/requiring treatment or stopping clinical trial participation) are considered adverse events.

An adverse drug reaction means the causal relationship with clinical trials medication is clear, relevant, susceptible, less relevant, irrelevant and unable to evaluate to include the causality with clinical trials medications, which are clear, relevant and susceptible.

TEAE will be analyzed at the end of the study 4W +/- 5 days.

- All adverse events/adverse drug reactions
- All the characteristics of adverse events such as result, causality, severe, action taken etc according to the CRF order.
- All serious adverse events/adverse drug reations
- All solicited adverse events/adverse drug reations

2) Laboratory Test

The following tests will be collected by evaluating the status of the subject as normal/abnormal(CS:Clinically Significant and NCS: Non-Clinically Significant) and examination values.

- Hematological test – WBC, RBC, Hemoglobin, Platelets
- Blood biochemical test - Total Protein, Albumin, Total Bilirubin, AST, ALT, ALP, Total cholesterol, Serum creatinine
- Urinalysis – Protein, Glucose, Blood, Ketones

3) Anaphylaxis

The following tests will be collected by evaluating the status of the subject as normal/abnormal(CS:Clinically Significant and NCS: Non-Clinically Significant) and examination values.

- C3a
- C4a
- Mast Cell Tryptase

4) Inflammatory cytokine

The following inflammatory makers will be collected by evaluating the status of the subject as normal/abnormal(CS:Clinically Significant and NCS: Non-Clinically Significant) and examination values.

- IL-1b
- IL-2
- IL-6
- TNF-α

5) Vital Signs

The subject will be collected by evaluating the status of the subject as normal/abnormal(CS:Clinically Significant and NCS: Non-Clinically Significant) and examination values.

- Pulse rate(beats/min)
- Systolic Blood Pressure(mmHg)
- Diastolic Blood Pressure(mmHg)
- Temperature(℃)

6) Physical Examination

The subject will be collected by evaluating the status of the subject as normal/abnormal(CS:Clinically Significant and NCS: Non-Clinically Significant).

- General appearance
- Skin and mucous membranes
- Eyes
- Ears, nose, throat
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genito-urinary
- Neurological
- Musculo-skeletal
- Lymph nodes
- Obstetrics
- Gynecology
- Others.

3.2.2 Secondary endpoints (Efficacy endpoint)

1) The percentage of negative patients in the first blood culture after dosing of the study drug
   - Patients who had successfully treated *S.aureus* bacteremia in the final treatment evaluation in the first blood culture.
2) The percentage of patients who died due to *S.aureus* bacteremia by Day 14
   - Patients who died from *S.aureus* bacteremia within 14 days (From screening to Day 14).
3) The percentage of *S.aureus* bacteremia treatment failure (when blood cultures by Day 14 did not produce two consecutive negative results) by Day 14
   - Patients who had unsuccessfully treated *S.aureus* bacteremia in the final treatment evaluation in two consecutive blood culture.

3.2.3 Additional endpoint (Efficacy endpoint)

1) The percentage of patients who were satisfied both the survival at day 14 and the two consecutive negative blood culture results at day 14.
2) The percentage of patients who were not increased in dose level or frequency of the background medications* usages by day 14

   * It is mandatory concomitant medication, refer to section 11.7.1 of the protocol.
3) The percentage of patients with survival, two consecutive negative blood culture at day 14, and no increased in dose level or frequency of the background concomitant medications usages.

3.3 General Consideration of Statistical Analysis

- All report output and summary will be produced using SAS Version 9.4 or a later version and all the analysis will conduct after DB Lock .
- Continuous variables will be summarized in terms of the mean, standard deviation (SD), median, minimum (Min), maximum (Max), and number of subjects(N).
- Categorical variables will be summarized in terms of the number of subjects providing data at the relevant time point (N), frequency count, and percentages.
- Methods for medical coding
  All medical history/ adverse event will be classified according to the system organ class and the preferred term of Medical dictionary for Regulatory Affairs (MedDRA) latest version.
  Prior and concomitant medication will be summarized in frequency tables by Anatomical Therapeutic Chemical(ATC) drug class.
- There will be no imputation of missing data.
- Statistical tests
  All statistical analyzes will be performed a two-sided test at a significance level of 5%, 95% CI and a P-value will be reported
- Interim analysis
  An interim analysis will be conducted when the number of subjects who have finished participating in clinical trials is 28 or more (but less than 32) to evaluate the safety. The interim analysis will be performed for exploratory purposes by IDMC statistician. The interim analysis will be conducted all the contents of statistical analysis according to the Chapter 3.4 in section 3.4.3 and 3.4.4. There is no plan to stop the study early for the overwhelming efficacy, so there is no need to adjust the alpha level 0.05 for the final analyses.
- Subgroup analyses
  All the safety and efficacy tables will be produced under MRSA, and MSSA separately if the number of patients in MRSA and MSSA confirmed meaningful before the DB lock.

3.4 Statistical Analysis Method

3.4.1 Subject Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. The subject disposition summaries include the following:

1) For the study subject, a schematic diagram and a table should be presented so that the registration status including the screening and the dropout can be known.
2) The study subjects were classified into Safety set and Full Analysis set.
3) The table shows the distribution of the subjects who have violated the clinical trial plan and dropped out, and reason of discontinuation.

3.4.2 Demographic and Baseline variables

An analysis of baseline characteristics such as demographic information of the subjects of the clinical trials is performed on the safety analysis set.

The demographic and baseline of the subjects included in this study will be evaluated according to the treatment group. The continuous variables will be expressed as mean, standard deviation, minimum and maximum values, and the frequency and the ratio of the categorical variables will be obtained.

[Demographic]

- Age (years)
- Sex
- Height (cm)
- Weight (kg)

[Medical history]

- Prior-medical history:With in the past one year based on screening date.
- Current-medical history: Of all the collected medical history, excluded the prior medical history.

■ The disease name of the collected medical history is classified into SOC and PT using MedDRA(Latest version), and the number of subjects, percentage, and frequency are presented.

[Medication]

- Concurrent Medications should be collected within 1 month of the date of the screening visit or the medication currently being administered.
- Drugs taken prior to drug administration for this clinical trial should be analysed by reclassification of the prior-medications and concurrent-medication.
- Background medication: Essential concomitant medication which is the standard treatment for persistent bacteremia of *S. aureus*, is used in combination.

■ In WHO ATC(Latest version), indicate the number and percentage of the subjects, frequency of occurrence based on stage 1(Anatomical) and stage 2(Treatment).

3.4.3 Primary endpoint (Safety endpoint)

Safety analysis will be performed on Safety set.

■ Adverse event
■ Analyze all AE/ADR in the subject undergoing the clinical trials.
■ Analyze serious and caused of drop-out AE/ADR after administrations clinical trials medication.
■ Analyze solicited AE/ADR
■ Adverse event will be presented the number of subjects, percentages with 95% confidence intervals and frequency by treatment groups.
■ Adverse event which is classified with system organ class (SOC) and the preferred term (PT) of MedDRA(Latest Version) will be presented the number of subjects, percentages and frequency by treatment groups.
■ The severity, causality, action taken related to the study drug, action taken and observed result of AE/ADR will be presented as frequency of events by treatment groups.
■ All adverse events will be presented in the table including the following information by patients.
  - Subject number, verbatim of adverse event, SOC, PT, date of onset, date of resolution, severity, status of SAE, outcome, causality, action taken.

1) Laboratory Test

Laboratory test at the screening visit, visit2, visit7, visit 14, follow-up visit, changes before and after treatment

will be summarized as mean, standard deviation, minimum and maximum values by treatment groups.

For continuous variables, independant t-test or Wilcoxon rank sum test will be performed in order to identify statistically significant difference by treatment groups. Paired t-test or Wilcoxon's signed rank test will be performed to test the difference between the changes before and after treatment.

For categorical variables, Mcnemar's test(or Bowker's test) will be performed to test the difference between the changes before and after treatment. Gernerized Estimating Equation (GEE) will be performed in order to identify statistically significant difference for changes of each treatment groups. Shift tables from the baseline to post-treatment visits will be provided for normal and abnormal lab parameters with CMH test for the treatment difference.

2) Anaphylasis test

Anaphylasis test at the visit 1 before treatment, visit1 after treatment, visit7, visit 14, additional follow-up visit, changes before and after treatment will be summarized as mean, standard deviation, minimum and maximum values by treatment groups.

For continuous variables, independant t-test or Wilcoxon rank sum test will be performed in order to identify statistically significant difference by treatment groups. Paired t-test or Wilcoxon's signed rank test will be performed to test the difference between the changes before and after treatment.

For categorical variables, Mcnemar's test(or Bowker's test) will be performed to test the difference between the changes before and after treatment. Gernerized Estimating Equation (GEE) will be performed in order to identify statistically significant difference for changes of each treamtment groups

3) Inflammatory cytokine test

Inflammatory cytokine test at the visit 1 before treatment, visit1 after treatment, visit7, visit 14, additional follow-up visit, changes before and after treatment will be summarized as mean, standard deviation, minimum and maximum values by treatment groups.

For continuous variables, independant t-test or Wilcoxon rank sum test will be performed in order to identify statistically significant difference by treamtment groups. Paired t-test or Wilcoxon's signed rank test will be performed to test the difference between the changes before and after treatment.

For categorical variables, Mcnemar's test(or Bowker's test) will be performed to test the difference between the changes before and after treatment. Generalized Estimating Equation (GEE) will be performed in order to identify statistically significant difference for changes of each treamtment groups

4) Vital signs

Vital signs at the screening visit, visit 1, visit7, visit 14, follow-up visit and additional follow-up visit, changes before and after treatment will be summarized as mean, standard deviation, minimum and maximum values by treatment groups.

For continuous variables, independant t-test or Wilcoxon rank sum test will be performed in order to identify statistically significant difference by treamtment groups. Paired t-test or Wilcoxon's signed rank test will be performed to test the difference between the changes before and after treatment.

For categorical variables, Mcnemar's test(Bowker's test) will be performed to test the difference between the changes before and after treatment. Generalized Estimating Equation (GEE) will be performed in order to identify statistically significant difference for changes of each treatment groups

5) Physical Examination

Based on the screening criteria, perform the physical examinations including complications and present the number and percentage of subjects to be tested for normal and abnormal(CS, NCS) including complications.

For categorical variables, Mcnemar's test(Bowker's test) will be performed to test the difference between the changes before and after treatment. Generalized Estimating Equation (GEE) will be performed in order to identify statistically significant difference for changes of each treatment groups

3.4.4 Secondary endpoints (Efficacy endpoint)

All efficacy analysis will be performed on FA set.

1) Efficacy endpoint ①

■ The percentage of patients in the first blood culture negative after dosing of the study drug

- The percentage of patients who were negative in the first blood culture after the administration of the clinical trial drug. The descriptive statistics for each treatment group are presented for the percentage of negative patients (negative rate) in the first blood culture after administration of the therapeutic drug.
- Chi-squared test or fisher's exact test will be performed to test the difference success rate between the treatment groups.

2) Efficacy endpoint ②

■ The percentage of patients who died due to *S.aureus* bacteremia by Day 14

- Bacteremia (from the first bacteremia confirmation) on Day 14, the percentage of patients who died from *S. aureus* bacteremia and the descriptive statistics of the treatment group for *S. aureus* bacteremia mortality by day 14 are presented and evaluated.
- Chi-squared test or fisher's exact test will be performed to test the difference mortality rate the treatment groups.

3) Efficacy endpoint ③

■ The percentage of *S.aureus* bacteremia treatment failure (when blood cultures by Day 14 did not produce two consecutive negative results) by Day 14

- The descriptive statistics for the failure rate of *S.aureus* bacteremia until Day 14 (when no two consecutive negative events occurred in the blood cultures up to Day 14) and the failure rate of *S.aureus* bacteremia until Day 14 were presented and evaluated.
- Chi-squared test or fisher's exact test will be performed to test the difference failure rate between the treatment groups.

3.4.5 Additional endpoints (Efficacy endpoint)

All efficacy analysis will be performed on FA set.

■ The percentage of patients who were satisfied both survival at day 14 and two consecutive negative blood culture results at day 14.

- The percentage of patients who were satisfied both survival at day 14 and two consecutive negative blood culture results at day 14. The descriptive statistics for each treatment group are presented for the percentage of satisfied both survival at day 14 and two consecutive negative blood culture results at day 14.
- Chi-squared test or fisher's exact test will be performed to test the difference success rate between the treatment groups.

■ The percentage of patients who were not increased in dose level or frequency of the background medications usages by day 14

- The descriptive statistics for each treatment group are presented for the percentage of patients who were not increased in dose level or frequency of the background medications usages by day 14
- Chi-squared test or fisher's exact test will be performed to test the difference success rate between the treatment groups.

■ The percentage of patients who were satisfied both survival at day 14, two consecutive negative blood culture results at day 14 and no increasing in dose level or frequency of the background concomitant medications

- The descriptive statistics for each treatment group are presented for the percentage of patients who were satisfied both survival at day 14, two consecutive negative blood culture results at day 14 and no increasing in dose level or frequency of the background concomitant meds
- Chi-squared test or fisher's exact test will be performed to test the difference success rate between the treatment groups.

4 Adjusted Statistical Analysis Method

There is no change in the statistical analysis method, endpoint and analysis method related background medication have added on 3.2.3 and 3.4.5 sections.

5 Reporting Conventions

- All statistical analysis results will be presented in tables or figures to help understand the data of this study.
- Continuos data will be summarized in terms of the mean, standard deviation (SD), median, minimum (Min), maximum (Max), and number of observations(N).
- Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (N), frequency count, and percentages.
- If the results is derived as <xxx, >xxx, less than xxx, xxx or more, the value should be excluded and analyzed separately.
- The summary statistics such as mean, standard deviation (SD), minimum (Min) and maximum(Max) value are rounded to the third decimal place to represent the second decimal place.
- The number of subjects and frequency of occurrence are represented by intergers and the percentages will be rounded to the third decimal place to represent the second decimal place.
- The p-value from statistical test will be rounded to the fourth decimal place, rounded off to the fifth decimal place, and if the p-value is less than 0.0001, it shall be unified to '<0.0001'.

6 References

1. Study Protocol No.: ITB-101 (version 2.1, effective date: 2019. 05. 09))