STATISTICAL ANALYSIS PLAN

Study topic	A Multicenter, Randomized, Double-Blind, Comparative, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous Imipenem/Cilastatin-XNW4107 in Comparison with Imipenem/Cilastatin/Relebactam in Adults with Hospital-Acquired Bacterial Pneumonia or Ventilator-Associated Bacterial Pneumonia
Test drug name:	Imipenem/Cilastatin in Combination with XNW4107 for Injection
Study number	XNW4107-302
[redacted]	[redacted]
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	Acute Physiology and Chronic Health Evaluation
ALT	alanine transaminase
ALP	alkaline phosphatase
APACHE	Acute Physiology and Chronic Health Scoring System
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemistry
BAL	Bronchoalveolar lavage
BLQ	Below the lower limit of quantification
CE	Clinically Evaluable
CI	confidence interval
CRF	Case Report Form
CR-MITT	Carbapenem-resistant MITT
CSR	Clinical Research Reports
CV	Percentage coefficient of variation
DMC	Data Monitoring Committee
DRC	Data Review Committee
ECG	electrocardiogram
EDC	Electronic Data Acquisition
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
FU Day	follow-up day
GCS	Glasgow Coma Score
HABP	Hospital-acquired bacterial pneumonia
HLT	high level language
HLGT	high level grouping
ICU	intensive care unit
ID	serial number
IMI	Imipenem
IMI-XNW4107	Imipenem/cilastatin-XNW4107
IMI/REL	Imipenem/cilastatin/relabatan
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LFU	Late Follow-up
LLT	low level (i.e. not a high level tone)
LOQ	limit of quantification
logistic regression	logistic regression
ME	Microbiologically assessable
MedDRA	International Dictionary of Medical Terms
MIC	Minimum Inhibitory Concentration
micro-MITT	Microbiologic Modified Intent-to-Treat
MITT	Modified Intent-To-Treat
MRSA	Methicillin-resistant Staphylococcus aureus
PBS	protected brush specimen
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PT	preferred term

Q1, Q3	First quartile, third quartile
QT	The ECG interval between the onset of the Q wave and the termination of the T wave, representing the time at which ventricular depolarization and repolarization occur
QTc	QT interval corrected for heart rate
QTcF	Correction of QT intervals from heart rate using the Fredericia formula
RR	ECG intervals represent a measurement of the time between the R-wave of one heartbeat and the R-wave of the previous heartbeat
SAE	serious adverse event
SAF	Safe People
SAP	Statistical analysis plan
SD	(statistics) standard deviation
SE	standard error
SOC	Classification of system organs
SOFA	Sequential organ failure assessment
TEAE	treatment-emergent adverse event
TFL	Tables, graphs and lists
TOC	Test-of-Cure
ULN	upper limit of normalcy
VABP	ventilator-associated bacterial pneumonia
vHABP	mechanical ventilation for HABP
WHO	World Health Organization

1. SUMMARY

This Statistical Analysis Plan (SAP) describes the study XNW4107-302 (A Multicenter, Randomized, Double-Blind, Comparative, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous Imipenem/Cilastatin-XNW4107 in Comparison with Imipenem/Cilastatin/Relebactam in Adults with Hospital-Acquired Bacterial Pneumonia or Ventilator-Associated Bacterial Pneumonia) Clinical Study Report (CSR) statistical analysis methods and data used in Tables, Figures, and Lists (TFL). This SAP is based on the Clinical Study Protocol (V4.1) dated April 23, 2024 and the electronic Case Report Form (eCRF) version 8.0. The SAP will be finalized before the database is finally locked. Any changes made after the SAP is finalized will be documented in the CSR.

For the purposes of this SAP, test drug will be defined as Imipenem/Cilastatin-XNW4107 (IMI-XNW4107), control drug will be defined as Imipenem/Cilastatin/Relebactam (IMI/REL), and investigational drug will include both test and control drugs.

1.1. Research Objectives

1.1.1. Primary Objectives

- To evaluate the all-cause mortality rate through Day 14 post-randomization of subjects in the IMI-XNW4107 group compared to the IMI/REL group in the Modified Intent-to-Treat (MITT) population.

1.1.2. Secondary Objectives

Efficacy

- To evaluate the all-cause mortality rate through Day 28 post-randomization of subjects in the IMI-XNW4107 group compared to the IMI/REL group in the MITT population

- To evaluate the all-cause mortality rate through Day 14 and through Day 28 post-randomization of subjects in the IMI-XNW4107 group compared to the IMI/REL group in the Microbiologic MITT (micro-MITT) population, extended micro-MITT, clinically evaluable (CE), microbiologically evaluable (ME), and Carbapenem-resistant MITT (CR-MITT) populations

- To evaluate the clinical outcome of IMI-XNW4107 compared to IMI/REL at Day 4, End of Treatment (EOT), Test-of-Cure (TOC), and Late Follow-up (LFU) visits in the MITT, micro-MITT, extended micro-MITT, CE, ME, and CR-MITT populations

- To evaluate the microbiological outcome of IMI-XNW4107 compared to IMI/REL at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations

- To evaluate the by-pathogen microbiological outcome of IMI-XNW4107 compared to IMI/REL at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations

- To evaluate the overall outcome of IMI-XNW4107 compared to IMI/REL at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations.

Safety

- To evaluate the safety and tolerability of IMI-XNW4107 administered by IV infusion compared to IMI/REL in subjects with HABP or VABP in the Safety population (SAF).

Pharmacokinetics

- To evaluate the PK of IMI-XNW4107 in subjects with HABP/VABP, and to provide data for the population PK (PopPK) modeling and exposure-response modeling analysis in subjects with HABP or VABP.

1.1.3. Exploratory Objectives

Healthcare Utilization

- To determine healthcare utilization up to Day 28 post-randomization in the IMI-XNW4107 group compared to the IMI/REL group in the MITT population.

1.2. Study Design

This is a prospective, multicenter, double-blind, randomized, active-controlled study to evaluate the efficacy, safety, and tolerability of IMI-XNW4107 in comparison with IMI/REL in the treatment of adults with HABP/VABP caused by Gram-negative bacteria.

[redacted]

Approximately 450 subjects with a clinical diagnosis of HABP/VABP who meet all eligibility criteria, and assessed by the investigator as requiring 7 to 14 days of IV antibiotic treatment in the hospital will be randomized.

Randomization will be stratified by type of infection (non-ventilated HABP vs. ventilated HABP/VABP), Acute Physiology and Chronic Health Evaluation II (APACHE II) score (<15 vs. ⩾15), and country/region (China vs. Rest of World). At least 50% of enrolled subjects will be on mechanical ventilation at enrollment (VABP/ventilated HABP).

Subjects will be randomly assigned to study treatment in a double-blind manner in a 2:1 ratio via an Interactive Web/Voice Response System (IXRS) to receive either imipenem 500 mg/cilastatin 500 mg-XNW4107 250 mg (N=300) infused IV as a 30-minute infusion (±5 minutes) q6h (±30 minutes) or IMI/REL 1.25 g (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) (N=150) infused IV as a 30-minute infusion (±5 minutes) q6h (±30 minutes) for a recommended treatment duration of 7 to 14 days (judged by the investigator).

Dose adjustments will be required for subjects with abnormal renal function.

Concomitant treatment with optional linezolid (600 mg as an IV infusion over 30 to 120 minutes every 12 hours) as judged by the investigator can be given to subjects in both arms to provide coverage for methicillin-resistant Staphylococcus aureus (MRSA) as per local standard of care. The treatment duration of MRSA will be determined by the investigator. The recommended treatment duration for a confirmed MRSA infection is a minimum of 7 days, with a minimum of 14 days for MRSA bacteremia. Empiric linezolid treatment will be stopped if the final culture results from the baseline lower respiratory tract sample do not demonstrate the presence of MRSA. For subjects in whom linezolid cannot be used, IV vancomycin may be used.

In addition to all-cause mortality (survival) through Day 14 (primary endpoint) and through Day 28, assessments of clinical and microbiological outcomes will be performed at Day 4 (clinical outcome only), EOT (the last day of study treatment [+1 day]), TOC (Day 21 [±2 days]), and an LFU visit (Day 28 [±3 days]).

Figure 1.2-1 Study Design provides an overview of the study design.

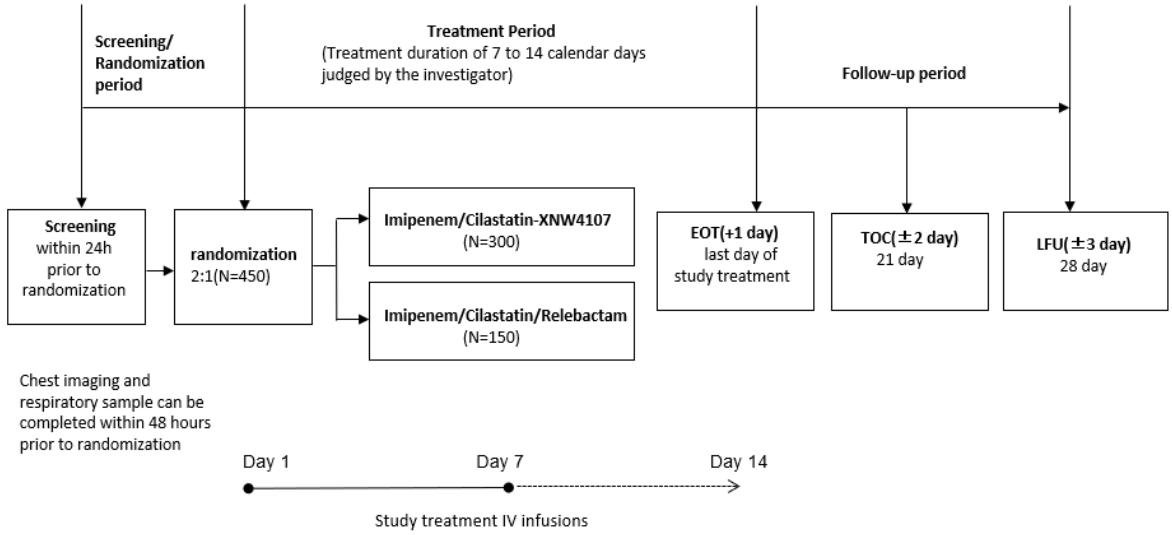


Figure 1.2-1 Study Design

1.3. Sample Size and Test Efficacy

Assuming an all-cause mortality rate of 10% for both treatment groups, a 2:1 randomization ratio, and a one-sided significance level of 0.025, a trial of 450 subjects will have more than 90% power to show non-inferiority with a 10% non-inferiority margin.

2. TYPES OF ANALYSIS PLANNED

2.1. Data Monitoring Committee Analysis

An independent DMC will be employed to oversee the progress of this study and to ensure the ongoing safety of the subjects participating in this study. The DMC will regularly review the safety data of enrolled subjects. The DMC can only recommend stopping the study early based on safety findings. No early stopping for efficacy is planned. Details describing the DMC process and procedures, and the timing and frequency of meetings will be outlined in a separate DMC Charter.

2.2. Data Review Committee Analysis

An independent DRC, which will be separated from the DMC, will be employed to perform the sample size re-estimation. This blinded sample size re-estimation is planned after approximately 300 subjects (approximately 67% of the planned recruitment) have been recruited, randomized, and had an opportunity to reach Day 14 to assess the blinded all-cause mortality rate (pooled across treatment groups) at Day 14 to ensure the study assumptions are as expected and will confirm if the initial sample size is adequate or an increase in sample size is required to ensure the study has adequate power for the primary outcome measure.

The DRC would recommend increasing the planned total sample size to have adequate power if the observed all-cause mortality rate (pooled across treatment groups) at Day 14 is more than 10%.

The calculated sample sizes for different assumptions of all-cause mortality rate with 2:1 randomization ratio for IMI-XNW4107 vs. IMI/REL are shown below.

Table 2.2-1 Sample sizes for different all-cause mortality rates

Non inferiority Margin	All-Cause Mortality Rate	Power	Total Sample Size	Increased Sample Size
10%	12.5%	90%	518	68
		85%	442	-8
	15%	90%	603	153
		85%	516	66
	20%	90%	757	307
		85%	647	197
	25%	90%	887	437
		85%	758	308

The DRC would make independent recommendation to the sponsor based on their data review.

It is important to note that no early termination for efficacy is planned for this study.

The discussion and decision will be appropriately documented using meeting minutes.

Details describing the DRC process and procedures will be outlined in a separate DRC Charter.

2.3. Final Analysis

The study will be unblinded and final analyses will be performed when all subjects have completed the study, unresolved challenges have been resolved or confirmed to be unresolvable, and data have been cleaned and locked.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

3.1. Data Handling

Descriptive statistics will be used to analyze the results. For categorical variables, the number and percentage of subjects in each category will be listed; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum and maximum values will be listed.

Unless otherwise stated, all statistical tests are two-sided with a significance level of 5%.

The number of decimal places in which consecutive data are summarized:

- For minimum (min) and maximum (max) values, the number of decimal places displayed is the same as the data collected.
- Mean, median, geometric mean, first quartile (Q1), and third quartile (Q3), show one more decimal than the collected data. Standard Deviation (SD), Standard Error (SE), Confidence Interval (CI), and Coefficient of Variation Percentage (CV), show two more decimals than the collected data. Up to four decimals.
- For percentage data and its mean, median, first quartile (Q1), third quartile (Q3), minimum (min), maximum (max), standard deviation (SD), and standard error (SE), one decimal place is displayed.

P-value display:

- The P-value will be rounded to the nearest number using the decimal places specified below
  - P≥ At 0.0001, the p value is reported to 4 decimal places.
  - For $p < 0.0001$, report $p < 0.0001$.
  - If $p > 0.9999$, then report > 0.9999.

The list of all subjects will be sorted by subject number, date and time of visit (if applicable). Data collected on the recording form (e.g., AE) will be listed chronologically among subjects. The treatment group to which the subject was randomly assigned (initial assignment in the IRT system) will be used when listing the intent-to-treat (ITT) population, and the treatment group to which the subject was actually treated (in the EDC) will be used when listing the safety population\pharmacokinetic population. Age, sex at birth, race and ethnicity will be included in the listings.

3.2. Analysis Population

The analysis population defines the subjects included in the analysis. This section contains all analytic populations and their definitions. The subjects included in each population will be determined prior to the unblinding analysis. All tables, figures, and lists will be subtitled with the corresponding analysis population.

For each population, the number and percentage of subjects eligible for inclusion will be summarized by treatment group, as well as the number and percentage of subjects excluded and their primary reason for exclusion.

Subjects who are randomized will be defined as subjects who have filled out the randomization information on the CRF D1 visit randomization page.

3.2.1. Intent-to-treat (ITT) Population

All subjects who are randomized. Subjects are analyzed according to the randomized treatment, regardless of the treatment actually received.

3.2.2. Safety Population (SAF)

All subjects who receive at least 1 dose of study drug during the study. Subjects are analyzed according to the treatment received during the study.

3.2.3. Modified Intent-to-Treat (MITT) Population

The MITT population will serve as the primary population for efficacy analyses in this study. The MITT population is defined as all subjects from the ITT who receive at least 1 dose of study drug.

3.2.4. Microbiologic Modified Intent-to-Treat (micro-MITT) Population

The micro-MITT population is defined as all subjects from the MITT who have a Gram-negative pathogen identified at baseline and the pathogen is susceptible to the investigational medicinal product and comparator.

For cases where multiple gram-negative pathogens (plural organisms) were identified at baseline, all pathogens were only included in micro-MITT if they were susceptible to the test and control drugs.

Only pathogenic bacteria identified in lower respiratory tract samples were considered.

The rules for the processing and derivation of microbiological data, as well as related definitions, are detailed in Section 3.6.2.

3.2.5. Carbapenem-resistant Modified Intent-to-Treat (CR-MITT) Population

All subjects from the MITT who have a baseline Gram-negative pathogen identified which is resistant to any carbapenem.

Any one pathogen resistant to any carbapenem antibiotic can be included in the CR-MITT population.

Only pathogenic bacteria identified in lower respiratory tract samples were considered.

The rules for the processing and derivation of microbiological data, as well as related definitions, are detailed in Section 3.6.2.

3.2.6. Extended Microbiologic Modified Intent-to-Treat (extended micro-MITT) Population

All subjects from the MITT who have a baseline Gram-negative pathogen identified which is susceptible to either the investigational medicinal product or comparator.

Gram-negative pathogens identified in the extended micro-MITT population need to have at least one susceptible to the test drug or control drug.

Only pathogenic bacteria identified in lower respiratory tract samples were considered.

The rules for the processing and derivation of microbiological data, as well as related definitions, are detailed in Section 3.6.2.

[redacted]

3.2.8. Clinically Evaluable (CE) Population

All subjects from the MITT who receive at least 72 hours of IV study treatment, have an appropriate diagnosis of HABP/VABP, have no important protocol deviations that would affect the assessment of clinical outcome, and have no missing nor indeterminate assessment of clinical outcome.

Based on the above definition, subjects who meet all of the following criteria will be included in the CE population:

- Duration of exposure to study drug≥ 72 hours .
- Meets Inclusion Criterion 4: Has HABP or VABP, as defined below, requiring intravenous antimicrobial therapy. Note: HABP is defined as symptoms of acute bacterial pneumonia occurring at least 48 hours after hospitalization or within 7 days of discharge from an acute or chronic care facility (e.g., long term care, rehabilitation center, hospital or skilled nursing home). Subjects may have developed acute respiratory failure requiring mechanical ventilation for HABP (vHABP). VABP is defined as acute bacterial pneumonia for which the subject has received mechanical ventilation via endotracheal (or transnasal tracheal) intubation or tracheotomy for ≥48 hours.
- Subjects who do not meet Exclusion Criterion 2: Subjects with known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia including novel coronavirus pneumonia (COVID-19), or chemical pneumonia (including

aspiration of gastric contents, inhalation injuries).

- No sustained discontinuation of the test drug≥ for 48 hours (if discontinued and total number of discontinuations< 8).
- No co-prohibition of systemic gram-negative antibiotics for ≥ 72 hours (screened based on concomitant medication and co-prohibition regimen deviation data).
- No EOT or TOC Clinical Assessments Uncertain/Missing (Clinical Assessments at EOT and TOC visits may not be Uncertain or Missing. Note: Death resulting in a clinical assessment not being collected is not considered missing).

3.2.9. Microbiologically Evaluable (ME) Population

All subjects in micro-MITT who received at least 72 hours of intravenous study treatment, had an appropriate diagnosis of HABP/VABP, had no significant protocol deviations that could affect the microbiologic efficacy evaluation, and had no microbiologic efficacy evaluations that were missing or inconclusive.

Based on the above definition, subjects who meet all of the following criteria will be included in the ME population:

- Eligible for micro-MITT population.
- Duration of exposure to the study drug≥ 72 hours.
- Meets Inclusion Criterion 4: Has HABP or VABP, as defined below, requiring intravenous antimicrobial therapy. Note: HABP is defined as symptoms of acute bacterial pneumonia occurring at least 48 hours after hospitalization or within 7 days of discharge from an acute or chronic care facility (e.g., long term care, rehabilitation center, hospital or skilled nursing home). Subjects may have developed acute respiratory failure requiring mechanical ventilation for HABP (vHABP). VABP is defined as acute bacterial pneumonia in subjects receiving mechanical ventilation via endotracheal (or transnasal tracheal) intubation or tracheotomy for ≥48 hours.
- Subjects who do not meet Exclusion Criterion 2: Subjects with known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia including novel coronavirus pneumonia (COVID-19), or chemical pneumonia (including aspiration of gastric contents, inhalation injuries).
- No sustained discontinuation of the test drug≥ for 48 hours (if discontinued and total number of discontinuations< 8).
- No co-prohibition of systemic gram-negative antibiotics for ≥ 72 hours (screened based on concomitant medication and co-prohibition regimen deviation data).
- No EOT or TOC microbiologic evaluations are indeterminate/missing (Evaluation of microbial efficacy at EOT and TOC visits may not be indeterminate/missing. (Note:

Lower respiratory tract samples are not collected at the EOT/TOC/LFU visit, and microbial efficacy is assessed on the basis of clinical efficacy results and is not missing).

- Only pathogenic bacteria identified in lower respiratory tract samples were considered.

3.2.10. Pharmacokinetic (PK) Population

All subjects from the SAF during the study with at least 1 reportable concentration of XNW4107, imipenem, or cilastatin.

The PK population was judged only for the study drug treatment group.

3.3. Subject Grouping

When analysis is performed based on the ITT, MITT populations, subjects will be grouped according to the treatment they were randomized to receive. For analyses based on the SAF, micro-MITT, CR-MITT, extended micro-MITT, CE, ME, and PK populations, subjects will be grouped according to the treatment they actually received. The actual treatment group received will differ from the randomly assigned treatment group only if all of the study or control medications actually received by the subject throughout the treatment period are different from the randomly assigned medications.

3.4. Stratification Factors and Covariates

Subjects will be randomly assigned to treatment groups in a 1:1 ratio (Protocol V1.0) and a 2:1 ratio (Protocol V3.3 and beyond) using stratified randomization via an interactive voice or web-based response system (IRT). Stratification will be based on the following variables:

- Type of infection (non-ventilated HABP vs. ventilated HABP).
- Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (<15 versus ≥15).
- Country/Region (China & Rest of the World).

If there is a difference in the stratification factors between the IRT and the EDC, the value recorded in the EDC will be used in the analysis. In addition, this difference will be presented in the statistical analysis.

For efficacy endpoints, stratification variables will be included as covariates in the efficacy analysis model.

3.5. Missing Data and Outliers

3.5.1. Missing Data

As a general rule, missing data are not filled in unless otherwise specified. The exceptions are listed below.

Section 9.1.5.2 describes how to handle missing or incomplete AE start dates. The treatment of prior and concomitant medications is described in Section 7.1. For missing primary estimate target analyses, the fill rules are described in Section 8.1.2. For missing microbiologic data, the fill rule is described in Section 3.6.2. For missing clinical outcomes, microbiologic outcomes, and overall assessment results, the rules for filling in are described in Sections 8.2.2.1, 8.2.3.1, and

8.2.4.1. Sections 8.3.1 and 5.2 describe the treatment of incomplete dates for exploratory endpoints. Details of the filling of these missing data can be found in the relevant sections of this document.

3.6. Data Processing and Derivation Rules

The rules regarding PK data are detailed in chapter 10.

3.6.1. Safety and Efficacy Data

Continuous safety and efficacy and data will be filled in as follows:

- If the data is reported as <x", a value 1 unit less than x will be used to calculate the descriptive statistic. For example, if the reported values are< 50 and< 5.0, then 49 and 4.9, respectively, will be used to calculate the summary statistic. An exception to this rule is if the reported value is< 1 or< 0.1, etc. If the reported value is< 1 or< 0.1, then 0.9 or 0.09 will be used to calculate the summary statistic, respectively.
- If the data is reported as "> x", a value 1 unit greater than x will be used to calculate the descriptive statistic. Values with a decimal point will follow the same logic as above. For subjects with O2 saturation, Basophils, Eosinophils, Hematocrit, Lymphocytes, Monocytes and Neutrophils, the percentages will be calculated. Neutrophils, with the maximum percentage not exceeding 100%.
- If the data are reported as ≤x" or ≥x", x will be used to calculate descriptive statistics.

3.6.2. Microbiology Data

Microbiology data include blood cultures and lower respiratory sample cultures. Microbiological sample collection and manipulation are detailed in the sample manipulation manual.

Statistical analysis of microorganisms associated with lower respiratory tract samples is based on samples collected by BAL, mini-BLA, or PBS, as well as qualifying endotracheal aspirates and coughed sputum (which should meet <10 squamous epithelial cells and >25 neutrophils). Definitions of eligibility are detailed in section 7.5.6.2 of the clinical protocol. During bacteremia analysis, any pathogenic organism detected in blood culture samples will be defined as bacteremia (with the following blood isolates considered non-pathogens: Corynebacterium spp., Propionibacterium spp. [with the exception of Propionibacterium acnes] and other diphtheroid; as well as Bacillus spp.)

The susceptibility of the pathogenic bacteria to the test drug and/or the control drug will be analyzed based on the results of the central laboratory drug sensitivity assay.

The susceptibility of the test drug IMI-XNW4107 was determined according to the provisional fold point of IMI-XNW4107, a β-lactamase inhibitor, which acts in combination with imipenem by restoring the activity of imipenem. Therefore, the interim discount points for IMI-XNW4107 against Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii were

determined according to the CLSI discount points for imipenem (1, 2, and 2 ug/mL, respectively). Previous population pharmacokinetic and Monte Carlo simulation analyses of the probability of attainment of the antimicrobial PK/PD target values support a >90% probability of attainment of the PK/PD target values at these interim fold points for all dose-delivery groups in the XNW4107-302 study. For other pathogenic bacteria, the highest provisional fold point (2 ug/mL) was determined for these 3 pathogens. That is, susceptibility was determined at MIC=2 ug/mL for all pathogenic bacteria except for Escherichia coli, for which susceptibility was determined at MIC=1 ug/mL. If the minimum inhibitory concentration (MIC) of the test drug (IMI-XNW4107) for a particular pathogen ≤ break point, the test drug will be determined to be sensitive for that pathogen.

For all pathogens missing IMI/REL susceptibility data, impute using IMI susceptibility results (only for pathogens with IMI susceptibility reported as Susceptible [S]. Specifically: if IMI/REL susceptibility is missing but IMI susceptibility data exists and is Susceptible [S], then IMI/REL susceptibility for that pathogen shall be imputed as Susceptible [S]).

The analysis related to microbiological data is mainly based on the test results of the central laboratory, and if the pathogen names of the local laboratory and the central laboratory are different, the pathogen names of the central laboratory are used for analysis. However, if the pathogen name is identified in the local laboratory data but not mailed to the central laboratory for various reasons, the pathogen name reported by the local laboratory is used for filling. In this case, the MIC will be considered unknown. For pathogens sent repeatedly by the local laboratory, if the names of the pathogens are consistent between the two mailings (using the name tested by the central laboratory), use the first mailing of pathogen data; if the names of the pathogens are not consistent between the two mailings, use the second mailing of pathogen data.

Definition of carbapenem-resistant pathogens: pathogenic bacteria that are resistant to any of the imipenem or meropenem carbapenem antimicrobials.

3.7. Analyzing the Interview Window

3.7.1. Definition of Study Day

Study days will be calculated from the subject's randomization date using the following formula:

- Post-randomization study day: assessment date - randomization date + 1
- Study day before randomization: assessment date - randomization date

Thus, study day 1 refers to the date of randomization.

3.7.2. Definition of Follow Up Day

Follow-up days will be defined as the number of days after the last dosing date (FU Day 0) and will only be counted if the collection date is on or after the last dosing date, which will be calculated as follows:

Follow-up day = Date of collection - Last date of administration

3.7.3. Definition of Baseline

Unless otherwise noted, baseline will be defined as the last non-missing outcome prior to the first dose.

For results that were collected on the date of the exam, but not at the time, the screening period will be considered to have occurred prior to the D1 visit in the calculation. For chest imaging results, and microbiology sample culture results, the time of collection needs to be within the time window specified in the following scenarios, and anything beyond that will not be included in the calculation of the baseline.

- Imaging is acceptable for results within 48h prior to randomization;
- Microorganisms can be accepted as samples within 48h prior to randomization to assess contamination not as a baseline.

3.7.4. Analysis Visit Windows

Subject visits may be conducted beyond the window (i.e., beyond the date specified in the protocol), but data collected should be as of the time of that visit requirement (e.g., survival at D28 may be conducted at D30 but collected at D28 and earlier), and the efficacy and safety analyses will be conducted using the nominal visit as documented on the CRF (according to the protocol).

3.7.5. Selection of Data in the Event of Multiple Records in an Analysis Visit

Depending on the method of statistical analysis, only a single value may be required under each nominal visit. For example, a single value is usually required for the change from baseline across visits; whereas for time-to-event analyses, a single value per analytical window is not required.

3.7.5.1. Safety Data

If multiple valid, non-missing measurements exist for each visit, but only a single value is needed, the record will be selected based on the following rules:

- For baseline, the last non-missing value prior to the time of the first administration of the study drug will be selected unless otherwise stated; if no time was recorded, or a time is missing, the value of the last non-missing time prior to the date of the first administration will be selected for inclusion in the calculation. If there are multiple records on the same day with the same time or with no time recorded, the mean value will be the baseline value for continuous data, and for categorical data, the result with the lowest severity (e.g., for electrocardiogram [ECG] safety results, a normal rather than an abnormal result will be selected) will be the baseline value.
- For post-baseline values (only results from nominal visits were considered):

- The record closest to the nominal study date for that visit (for EOT visits, the nominal study date is the last date of administration) will be selected.
- If 2 records are equidistant from the nominal study date, the record with the later study date is selected.
- If there was more than 1 record on the selected study day, the average was taken for continuous data and the most severe record for categorical data, unless otherwise stated.

3.7.5.2. Microbiological Data

If multiple valid, non-missing measurements exist for each nominal visit, the records will be selected based on the following rules:

- For the baseline:
  - Lower respiratory sample cultures: culture results from the most recent non-missing collection of samples prior to the time of first administration of study drug will be selected. Microbiological samples within 48h prior to randomization are acceptable, isolates assessed as contaminated microbiological samples will not be used as a baseline.
  - Blood cultures: cultures of two recent (different site) blood microbiology samples collected prior to the time of first administration of study drug will be selected. Isolates from the cultures of both of these 2 blood microbiology samples will be used as a baseline. Culture results from blood microbiology samples collected from two different sites within 48h prior to randomization are acceptable. Isolates from blood microbiology samples assessed as contaminated will not be used as baseline.
- For post-baseline values:
  - Lower respiratory sample cultures: the results of all sample cultures collected within the nominal visit will be used.
  - Blood cultures: the results of all cultures of samples collected within the nominal visit will be used.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

Key study dates (first subject visit, first subject randomized, last subject randomized, last subject last visit) will be provided.

A summary of subject enrollment will be provided by treatment group for each country and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects with none missing value for that column.

Subject screening, screening failures and detailed reasons for screening failures will be summarized. Screening will be defined as all subjects who signed informed consent and reasons for screening failure will be summarized by inclusion or exclusion criteria.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of enrolled subjects. If there are discrepancies in the value used for stratification assignment between the IRT and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects who signed informed consent, the number of subjects randomized, the number of subjects randomized and treated, and the number of subjects in each of the categories listed below:

- ITT population
- SAF population
- MITT population
- Micro-MITT population
- CR-MITT population
- Extend the micro-MITT population
- CE population
- ME population
- PK population
- Completed treatment
- Discontinued treatment and Primary reason for treatment discontinuation
- Completed study

- Discontinued study and Primary reason for study discontinuation

For the primary reason of treatment and study discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety population corresponding to that column.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Primary reasons for treatment and study discontinuation
- Reasons for not randomization (will be provided by screening ID number in ascending order)
- Lot number and kit ID

4.2. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the ITT population. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the ITT population. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERIZATION

5.1. Demographics Baseline Characterization

Subject demographic variables (i.e., age [as a continuous variable, categorized as <65 years and≥ 65 years], sex, race, and ethnicity) and baseline characteristics (weight [in kilograms], height [in centimeters], and body mass index [in kilograms per meter^2]) were summarized by treatment group. Overall, summarization will be done using descriptive statistics for continuous variables and subject cases and percentages for categorical variables. Demographic data will be summarized based on safety and micro-MITT populations.

A list of subject demographics is provided in ascending order of subject number and includes the date of informed consent signing.

5.2. Other Baseline Characteristics Analysis

Other baseline characteristics include:

- Country/region (China and the rest of the world)
- Type of infection at baseline (non-ventilated HABP, mechanically ventilated HABP, VABP)
- APACHE II score (continuous variable)
- APACHE II scores (<10, 10 to <15 and≥ 15)
- Sequential Organ Failure Assessment (SOFA) score
- Glasgow Coma Scale (GCS) score (continuous variable)
- Glasgow Coma Scale (GCS) score (<7 and ≥7)
- Baseline ICU admission (yes/no/missing), i.e., ICU admission at the time of the first dose; if the ICU admission time is missing, the admission time is filled in using 00:00, and the ICU departure time is filled in using 23:59
- Baseline eGFR (continuous variable)
- Baseline eGFR (<30 mL/min, 30 to <60 mL/min, 60 to <90 mL/min, 90 to <150 mL/min, 150 to< 250 mL/min and≥ 250 mL/min)
- Baseline Liver Function (Normal, Abnormal), Abnormal liver function was defined as subjects with baseline results of any of the ALT, AST, ALP and total bilirubin in laboratory tests that were outside the normal range of values.
- Received antimicrobial therapy for this HABP/VABP (yes/no)
- Whether the subject received systemic or inhaled effective gram-negative antimicrobial medication for more than 24 hours sustained against a specific infection of HABP/VABP within 72 hours prior to randomization (Yes/No)
    - Whether the subject's previous antibiotic treatment was considered a clinical failure (yes/no), only if the answer to the above question was "yes".

  - Whether the subject required mechanical ventilation because of treatment failure (yes/no), only if the answer to the above question was "yes".
- Baseline lower respiratory tract gram-negative infections (no; yes: mono/poly)
- Top 5 ranking of respiratory pathogens in the lower respiratory tract at baseline HABP/VABP (5 most frequent in total groups)
- Resistance to gram-negative pathogenic bacteria of the respiratory tract at baseline (carbapenem-resistant/non-resistant)
- Concomitant bacteremia at baseline (yes/no)

These baseline characteristics will be summarized by test drug group, control drug group, and aggregate, using descriptive statistics for continuous variables and number and percentage of subjects for categorical variables. These baseline characteristics will be summarized based on the safety population and the micro-MITT population.

Also, baseline pathogens for the micro-MITT, extended micro-MITT, and CR-MITT populations will be summarized, as well as MIC results for IMI-XNW4107 and IMI/REL for these baseline pathogens. In this analysis, the MIC results for IMI-XNW4107 and IMI/REL for each baseline pathogen will be presented separately in the corresponding treatment groups, and the number of subject cases infected with the specific pathogen will be calculated, as well as the corresponding MIC_{50}, MIC_{90}, and MIC ranges.MIC_{50} and $MIC_{(90)}$ will be defined as being no less than 50% of the data and 90% of the data, respectively of the minimum value; MIC_{50} and MIC_{90} were calculated only if the number of subjects infected with a specific pathogen was 10 or more.

The rules for the processing and derivation of microbiological data, as well as related definitions, are detailed in Section 3.6.2.

Provides a list of other baseline characteristics of the subject, in ascending order of subject number.

5.3. Medical History

For medical histories collected during the screening period.

Based on the safety population, the number and percentage of subjects with a medical history were provided, and the number of cases and percentage of subjects with a medical history were summarized according to System Organ Classification (SOC) and Preferred Terminology (PT).

Provide a list of the subject's past medical history in ascending order of subject number.

5.4. Prior Antibacterial Drug Therapy

Prior antibacterial drug therapy will be collected at screening.

A by-subject listing of prior antibacterial drug therapy will be provided by subject ID number in ascending order.

5.5. Prior Medications (Antibacterial and Others)

Prior medications (antibacterial and others) will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

Prior medications (antibacterial and others) are defined as any medications taken before a subject took the first study drug. Prior medications were considered systemic gram-negative medications and included in the appropriate pooled analyses if their ATC codes appeared in the table below.

Table 5.5-1 Systemic Antimicrobial Medications Definitions

ATC 2	ATC 3	ATC 4	note
[redacted]			

Prior medications (antibacterial and others) will be summarized separately by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by ATC medical class and preferred term in the order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date/time prior to the first dosing date/time of study drug will be included in the prior medication summary regardless of when the stop date/time is. If a partial start date/time is entered the medication will be considered prior medications unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Population. No formal statistical testing is planned.

Specific by-subject listing of prior medications (antibacterial and others) will be provided by subject ID number in ascending order.

6. STUDY DRUG

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

6.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as following and will be expressed in days.

Duration of exposure to study drug = (last dose time - first dose time)/24 hour.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number and percentage of subjects exposed through the following time periods: 1 day, 2 days, ..., 14 days. Summaries will be provided by treatment group for the Safety Population

6.2. Adherence to Study Drug

The total number of doses administered and missed dose or dose interruption in clinical database will be summarized using descriptive statistics.

6.2.1. On-Treatment Adherence

The level of treatment period adherence to an investigational drug dosing regimen depends on the percentage of the total amount of investigational drug received by the subject relative to the total amount of investigational drug expected to be used under the investigational drug regimen during the subject's actual treatment period.

The total number of infusions of study drug and the total number of infusions of study drug expected to be used during the subject's actual treatment according to the study drug regimen will take into account the data in the EDC.

The level of adherence during the treatment period is expressed as a percentage and is calculated according to the following formula:

$$\text{On-Treatment Adherence（%）} = \left(\frac{\textit{Total Number of Study Drug Doses Administered}}{\textit{The total number of infusions of the study drug expected to be used according to the study drug regimen during the subject's actual treatment}}\right) \text{x } 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories (< 80%, ⩾ 80 to < 90%, ⩾ 90%) will be provided by treatment group for the Safety Population.

A by-subject listing of study drug administration will be provided by subject ID number (in ascending order) and visit (in chronological order).

7. CONCOMITANT MEDICATIONS (ANTIBACTERIALS AND OTHERS) AND DIAGNOSTIC/THERAPEUTIC PROCEDURES

Concomitant medications (antibacterials and others) will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.1. Combined Use of Non-Study Drugs (Antimicrobials and other Drugs)

Concomitant medications (antibacterials and others) are defined as medications taken while a subject took study drug. The definition of systemic gram-negative antibacterials is detailed in Section 5.5.

T Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for antibacterials and others separately. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by ATC medical class and preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day/time as the first dosing date/time or the last dosing date/time of study drug will also be considered concomitant. Medications with a stop date/time prior to the date/time of first dosing date/time of study drug or a start date/time after the last dosing date/time of study drug will be excluded from the concomitant medication summary. If a partial stop date/time is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries will be based on the Safety Population.

All concomitant medications (antibacterial and others) will be provided in a by-subject listing sorted by administration date in chronological order.

7.2. Treatment History (Non-Pharmacological)

Treatment history, i.e., diagnostic/therapeutic manipulation of combined non-pharmacological treatments will be summarized by System Organ Classification (SOC) and preferred terminology, and percentages will be calculated using the number of subjects in each

treatment group. When calculating the number of subjects and percentages, subjects reporting the same diagnostic/therapeutic maneuver multiple times will be counted only once. The summary table will be sorted in descending order of total frequency of SOC and preferred terms. For diagnostic/therapeutic operations with the same frequency, they will be sorted alphabetically.

Summaries will be based on the Safety Population.

All concomitant diagnostic/therapeutic procedures will be provided in a by-subject listing sorted by administration date in chronological order.

8. EFFICACY ANALYSIS

8.1. Primary Efficacy Endpoint

The primary endpoint is the Day 14 all-cause mortality rate in the MITT population.

8.1.1. Estimand for Primary Endpoint

8.1.1.1. Treatment

IMI-XNW4107 or IMI/REL given as IV infusions for a recommended treatment duration of 7 to 14 days.

8.1.1.2. Population

All subjects who underwent randomization and received at least 1 dose of study drug (MITT population).

8.1.1.3. Variable

Day 14 all-cause mortality rate after randomization.

8.1.1.4. Intercurrent Events and Handling Strategies

- Premature discontinuation of study treatment: based on treatment policy strategy, data after occurrence of intercurrent events will still be included in the analysis.
- Usage of rescue antibiotics: based on treatment policy strategy, data after occurrence of intercurrent events will still be included in the analysis.

8.1.1.5. Population-level Summary

Difference in Day 14 all-cause mortality rate after randomization between treatment groups (IMI-XNW4107 - IMI/REL).

8.1.2. Analysis Methods for Primary Estimand

8.1.2.1. Primary Efficacy Analysis

In order to determine whether IMI-XNW4107 is non-inferior to IMI/REL in subjects with HABP/VABP, a non-inferiority margin of 10% will be used, the study hypothesis to demonstrate noninferiority of IMI-XNW4107 to IMI/REL on all-cause mortality rate at Day 14 can be written as follows:

Null Hypothesis	$H_0: p_1 - p_2 > 10\%$
Alternative Hypothesis	$H_1: p_1 - p_2 \leq 10\%$

Where p_1 is the all-cause mortality rate for IMI-XNW4107 and p_2 is the all-cause mortality rate for IMI/REL.

Subjects with unknown survival status by Day 14 will not be considered as deaths for both treatment group.

The non-inferiority assessment will be based on the two-sided CI for the difference in proportions (IMI-XNW4107 minus IMI/REL). Stratified proportion difference along with its two-sided 95% CI using stratum-adjusted Mantel-Haenszel (MH) approach (Koch, 1989) stratified by

randomization stratification factors for treatment comparison (IMI XNW4107 group minus IMI/REL group) will be provided.

The stratified point estimates for the difference in proportions of subjects' all-cause mortality rate at Day 14 between IMI-XNW4107 group and IMI/REL group will be calculated using the following formula:

$$\hat{p}_1 - \hat{p}_2 = \frac{\sum W_h d_h}{\sum W_h}$$

Where $d_h = \hat{p}_{1h} - \hat{p}_{2h}$ is the difference in the proportion of subjects' all-cause mortality rate between IMI-XNW4107 group and IMI/REL group in stratum h $(h = 1, 2, \ldots, K)$, and $W_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$ is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample size of the IMI-XNW4107 group and IMI/REL group in stratum h, respectively.

The 95% stratum-adjusted MH CIs will be calculated using the following formula:

$$\hat{p}_1 - \hat{p}_2 \pm \mathrm{Z}_{1-\alpha/2} \cdot SE(\hat{p}_1 - \hat{p}_2)$$

Where $SE(\hat{p}_1 - \hat{p}_2) = \frac{\sqrt{\sum W_h^2 \left(\frac{\hat{p}^*_{1h}\left(1-\hat{p}^*_{1h}\right)}{n_{1h}-1} + \frac{\hat{p}^*_{2h}\left(1-\hat{p}^*_{2h}\right)}{n_{2h}-1} \right)}}{\sum W_h}$, $\hat{p}^*_{1h} = \frac{m_{1h}+0.5}{n_{1h}+1}$, $\hat{p}^*_{2h} = \frac{m_{2h}+0.5}{n_{2h}+1}$, and m_{1h} and m_{2h} are the number of subjects who experience all-cause mortality from the IMI-XNW4107 group and IMI/REL group in stratum h, respectively. $Z_{(1-\alpha/2)}$ is the 97.5% percentile of normal distribution with $\alpha = 0.05$.

Non-inferiority will be concluded if the upper limit of the two-sided 95% CI is less than or equal to 10%. If non-inferiority is demonstrated, a test for superiority will be performed, and superiority will be concluded if the upper limit of two-sided 95% CI is less than 0

8.1.2.2. Sensitivity Analysis

In the primary analysis, for both treatment groups, subjects with unknown survival at Day 14 will be considered missing. To evaluate the impact of missing data on all-cause mortality at Day 14, the following multiple fill method will be used:

Considering that within the same treatment group, within the same randomization stratification, subjects with unknown survival at day 14 and subjects with no deletions have similar outcomes, the data from all observed subjects with unknown survival at day 14 will be used to fill in subjects with unknown survival at day 14 in a multiple imputation method. A logistic regression model (logistic regression) will be used to generate the post-fill dataset, and the following covariates will be included in the model: treatment group (test drug vs. control drug), type of infection (non-ventilated HABP vs. ventilated HABP), and APACHE II scores (continuous variable). Newly generated datasets after filling were analyzed using the same methods as

described in Section 8.1.2.1. The results of these analyses were then finally combined using Rubin's Rule (Rubin's Rule) to derive the difference in proportions of the IMI-XNW4107 group minus the IMI/REL group and their two-sided 95% confidence intervals.

For the MITT population, the p-value from the stratified log-rank test comparing the IMI-XNW4107 group and the IMI/REL group will be provided, accompanied by Kaplan-Meier curves; the hazard ratio and its 95% confidence interval between the IMI-XNW4107 group and IMI/REL group will be calculated using a stratified Cox regression model.

8.1.2.3. Supplementary Analysis

[redacted]

For the results of the primary effectiveness analyses (both for subjects enrolled in China and outside of China), as well as the analyses described above for subjects enrolled in China, bar charts of Day 14 all-cause mortality by treatment group will be provided, along with estimated stratified proportional differences and their two-sided 95% CIs.

8.1.2.4. Subgroup Analysis

Day 14 all-cause mortality will be analyzed in the MITT population for the following subgroups

- Age (< 65 and≥ 65)
- Gender (male and female)
- Country/region (China and the rest of the world)
- Type of infection at baseline (non-ventilated HABP and ventilated HABP)
- Baseline APACHE II scores (<15 and≥ 15)
- ICU admission at baseline (yes/no)
- Baseline eGRF classification (<30 mL/min, 30 to <60 mL/min, 60 to <90 mL/min, 90 to <150 mL/min, 150 to <250 mL/min and ≥250 mL/min)
- Baseline liver function (normal, abnormal)
- Received antimicrobial therapy for this HABP/VABP (yes/no)
- Whether the subject's prior antibiotic therapy was considered a clinical treatment failure (yes/no)
- Baseline lower respiratory tract gram-negative infections (mono/poly)

- Top 5 Ranking of Respiratory Gram-Negative Bacteria under Baseline HABP/VABP (5 most frequent in combined dose groups)
- Resistance to gram-negative pathogenic bacteria of the respiratory tract at baseline (carbapenem-resistant/non-resistant)
- Concomitant bacteremia at baseline (yes/no)

For a subject, if the value of the grouping variable cannot be determined, this subject will be excluded from the corresponding subgroup analysis. Non-stratified risk difference between treatment groups will be evaluated for each of the subgroups. A forest plot will graphically present the non-stratified risk difference and 95% CI using normal approximation with a continuity correction on the treatment differences in the all-cause mortality rates at Day 14 between IMI-XNW4107 and IMI/REL for each of the subgroups. For both treatment groups, subjects with unknown survival at Day 14 will not be considered dead.

8.2. Secondary Efficacy Endpoint

The secondary endpoints for this study are the following:

- Day 28 all-cause mortality rate in the MITT population
- Day 14 and Day 28 all-cause mortality rate in the micro-MITT, extended micro-MITT, CE, ME, and CR-MITT populations
- The proportion of subjects with clinical success as evaluated by the investigator at Day 4, EOT, TOC, and LFU visits in the MITT, micro-MITT, extended micro-MITT, CE, ME, and CR-MITT populations
- The proportion of subjects with microbiological success at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, CR-MITT, and ME populations
- The proportional of subjects with microbiological success by pathogen at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations.
- The proportion of subjects with overall success at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations.

8.2.1. All-Cause Mortality Rate

The Day 14 and Day 28 all-cause mortality rate will be calculated as the percentage of subjects in each treatment group who experienced mortality, regardless of the cause, from randomization up to Day 14 or Day 28, the values recorded in the clinical database will be used for analyses.

8.2.1.1. All-Cause Mortality Rate Analysis

Day 14 and Day 28 all-cause mortality were analyzed in the different populations defined in Section 8.2 in a manner similar to the primary efficacy endpoints described in Section 8.1.2.1.

Provides a list of all-cause mortality rates for subjects at Day 14 and Day 28, in ascending order of subject number.

8.2.1.2. Subgroup Analysis of all-cause Mortality

All-cause mortality at Day 28 will be analyzed in the MITT population in subgroups similar to those described in Section 8.1.2.4.

8.2.1.3. By-pathogen All-cause Mortality Analysis

In the micro-MITT, extended micro-MITT, and CR-MITT populations, provide the proportion of subjects in each treatment group with all-cause mortality by pathogenic organisms at Day 14 and Day 28. For both treatment groups, subjects with unknown survival at Day 14 and Day 28 will not be considered dead.

In addition to the above analyses, in the micro-MITT, extended micro-MITT, and CR-MITT populations, the all-cause mortality rates at Day 14, and Day 28 will be presented for subjects in the corresponding dose groups by the species of Gram-negative pathogens detected in the subjects at baseline, for the MIC values of all detections at baseline IMI-XNW4107 and IMI\REL.

8.2.2. Clinical Outcomes

The assessment of clinical outcome will be assessed by the investigator using the clinical outcome criteria as outlined below and carried out on Day 4, EOT, TOC, and LFU visit.

The clinical response criteria up to TOC visit will be defined as follows:

- **Success**:
  - For Day 4 visit: a subject is alive with resolution or improvement in at least 1 baseline sign/symptom AND no worsening of any baseline signs/symptoms AND no development of new signs/symptoms of pneumonia requiring the initiation of a non-study antibacterial therapy for the index infection.
  - For EOT or TOC visits: a subject is alive with complete resolution or significant improvement of signs and symptoms that were present at baseline and no new signs/symptoms of pneumonia, such that no further antibacterial therapy is necessary.
- **Failure**:
  - For Day 4 visit, persistence or worsening of baseline clinical signs and/or symptoms or the development of new clinical signs and/or symptoms of pneumonia requiring the initiation of a non-study antibiotic therapy or death of the subject.
  - For EOT and TOC visits, persistence, incomplete resolution or no significant improvement of baseline clinical signs and symptoms of pneumonia, and the need for further antibiotic therapy or death of the subject.
- **Indeterminate**: Study data are not available for evaluation of clinical response for any reasons other than due to the lack of clinical improvement or death.

The clinical response criteria at LFU visit will be defined as follows:

- **Sustained success**: Clinical success at TOC and continued resolution or substantial improvement of baseline signs and symptoms of pneumonia, such that no antibacterial therapy has been required for the treatment of pneumonia between TOC and LFU.
- **Failure**: Subject previously assigned a clinical failure or indeterminate at TOC; or relapse defined as clinical success at TOC, but recurrence of signs/symptoms of pneumonia, appearance of new signs and/or symptoms of pneumonia between TOC and LFU, and further antibiotic therapy is warranted or death of the subject.
- **Indeterminate**: Study data are not available for evaluation of clinical response for any reasons other than due to the lack of clinical improvement or death.

The clinical outcomes recorded in the clinical database will be used for analyses.

8.2.2.1. By-Subject Clinical Outcomes Analysis

The proportions of subjects with clinical success as evaluated by the investigator at Day 4, EOT, TOC, and LFU visits will be provided for each treatment group together with the treatment difference and the corresponding CIs for the MITT, micro-MITT, extended micro-MITT, CR-MITT, CE, and ME populations.

Treatment differences for clinical success will be analyzed in a similar way to the primary efficacy endpoint described in Section 8.1.2.1.

Death will be considered as a clinical failure. Subjects with missing or indeterminate clinical responses will be considered failures in the analyses in the MITT, micro-MITT, extended micro-MITT, CR MITT and ME populations.

I In addition, the number and proportion of subjects having clinical outcome as success/sustained success, failure and indeterminate will be summarized by treatment group.

Provides a list of subjects' clinical outcomes, organized in ascending order by subject number.

8.2.2.2. By-Subject Clinical Outcomes Subgroup Analysis

Treatment for clinical success at D4, EOT, TOC, and LFU visits will be analyzed in the MITT population in subgroups similar to those described in Section 8.1.2.4.

8.2.2.3. By-Pathogen Clinical Outcomes Analysis

Proportion of subjects in the micro-MITT, extended micro-MITT, CR-MITT, and ME populations that provided clinical success by baseline pathogens at D4, EOT, TOC, and LFU exams for each treatment group.

In addition to the above analyses in the micro-MITT, extended micro-MITT, CR-MITT, and ME populations, the clinical cure rate at EOT, TOC, and LFU visits for subjects in the corresponding treatment groups will be listed by the species of gram-negative pathogens detected at baseline, and by the MIC values at baseline for IMI-XNW4107 and IMI\REL.

8.2.3. Microbiological Outcomes

Lower respiratory tract sample and blood culture data will be collected during the study and will be used in addition to the clinical response to programmatically assess the microbiological outcomes as defined below and carried out on EOT, TOC, and LFU visit.

- **Microbiological success** is based on the following rules:
  - **Eradication**: Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen.
  - **Presumed eradication**: Absence of appropriate post-baseline culture material in a subject, but judged to be a clinical success.
- **Microbiological failure** is based on the following:
  - **Persistence**: Continued presence of the baseline Gram-negative pathogen from an appropriate clinical specimen. Persistence at EOT or TOC will be carried forward.
  - **Presumed persistence**: Absence of appropriate post-baseline culture material in a subject, but judged to be a clinical failure.
  - **Recurrence**: Recurrence of the baseline Gram-negative pathogen from an appropriate clinical specimen taken after TOC and the TOC culture shows eradication.
  - **Indeterminate**: No culture obtained from an appropriate clinical specimen and no clinical outcome is determined.

Pathogens first appearing after baseline in subjects with a different baseline pathogen are categorized as described below and will be considered separately from microbiological response.

- **Superinfection**: Isolation of new pathogen(s) (other than the original baseline pathogen[s]) from an appropriate clinical specimen during treatment with study drug that is accompanied by new or worsening signs and symptoms of infection requiring alternative antimicrobial therapy
  - Superinfection were assessed at the EOT visit with the rule that new pathogens other than the original baseline pathogen were isolated from appropriate lower respiratory tract clinical samples during the EOT visit or prior study drug therapy and were clinically assessed as failures.
- **New infection:** Isolation of new pathogen(s) (other than the original baseline pathogen[s]) from an appropriate clinical specimen after completion of study drug treatment that is accompanied by new or worsening signs and symptoms of infection requiring alternative antimicrobial therapy.

  New infections are evaluated at the TOC and LFU visits with the rules:

- TOC visit: isolation of a new pathogen in addition to the original baseline pathogen from an appropriate lower respiratory tract clinical sample after the EOT visit, at or before the TOC visit, and a clinical assessment of failure;
- LFU visit: isolation of a new pathogen other than the original baseline pathogen from an appropriate lower respiratory tract clinical sample after the EOT visit, at or before the LFU visit, and a clinical assessment of failure.

- **Colonization**: Isolation of a new Gram-negative organism from a respiratory sample and no associated signs or symptoms of infection

  Colonization was evaluated at EOT, TOC and LFU visits with the rules:
  - EOT visit: isolation of new gram-negative pathogens in addition to the original baseline gram-negative pathogens from appropriate lower respiratory tract samples at or prior to the EOT visit, but assessed clinically as successful
  - TOC visit: isolation of new gram-negative pathogens in addition to the original baseline gram-negative pathogens from appropriate lower respiratory tract samples after the EOT visit and at or before the TOC visit, but assessed clinically as successful.
  - LFU visit: isolation of new gram-negative pathogens in addition to the original baseline gram-negative pathogens from appropriate lower respiratory tract samples after the TOC visit and at or before the LFU visit, but clinically assessed as successful.

The microbiological data will be analyzed for descriptive statistics by subject and pathogen classification.

8.2.3.1. Lower Respiratory Tract Sample Culture

Provide a list of the subject's lower respiratory tract sample cultures in ascending order of subject number.

8.2.3.2. Blood Culture

Provides a list of subject blood cultures, organized in ascending order by subject number.

8.2.3.3. By-Subject Microbiological Outcomes Analysis

Subject microbiological success was defined as all baseline infections with gram-negative pathogens were cleared.

The proportions of subjects with microbiological success at the EOT, TOC, and LFU visits will be provided for each treatment group together with the treatment difference and the corresponding CIs in the micro-MITT, extended micro-MITT, extended micro-MITT2, CR-MITT, and ME populations.

Treatment differences for microbiological success will be analyzed in a similar way to the primary efficacy endpoint described in Section 8.1.2.1.

Death will be considered as a microbiological failure. Subjects with missing or indeterminate microbiological responses will be considered failures in the analyses in the micro-MITT, extended micro-MITT, extended micro-MITT 2, and CR-MITT populations.

In addition, the number and proportion of subjects falling into each of the detailed microbiological outcome categories (Eradication, presumed eradication, persistence, presumed persistence, recurrence, indeterminate, superinfection, new infection and colonization) will be summarized by treatment group.

Provides a list of the microbiologic efficacy of the subjects, in ascending order of subject number.

8.2.3.4. By-Subject Microbiological Outcomes Subgroup Analysis

Treatment differences for microbiological success in the micro-MITT population at TOC visit will be analyzed in a similar way with the subgroup described in Section 8.1.2.4.

8.2.3.5. By-Pathogen Microbiological Outcomes Analysis

In the micro-MITT, extended micro-MITT, extended micro-MITT 2, CR-MITT, and ME populations, provide the proportion of subjects in each treatment group with microbiologic success and other microbiologic outcomes by pathogen on EOT, TOC, and LFU visits. Microbiological success will be summarized separately according to the subject's respective baseline Gram-negative pathogenic organisms. Other microbiological outcomes will be summarized according to the relative change of pathogenic bacteria after each baseline of the subjects.

In addition to the above analyses, in the micro-MITT, extended micro-MITT, CR-MITT, and ME populations, the microbiological success rate at EOT, TOC, and LFU visits for subjects in the corresponding treatment groups will be listed by the species of gram-negative pathogens detected at baseline, and by the MIC values at baseline for IMI-XNW4107 and IMI\REL.

8.2.4. Overall Outcomes

The overall outcome criteria are listed as the following:

- **Success**: Clinical success and microbiological success at the visits of EOT or TOC, or sustained success for clinical outcome and microbiological success at the visit of LFU. Microbiological success includes eradication or presumed eradication.

- **Failure**: Clinical failure and/or microbiological failure (persistence, presumed persistence or recurrence) at the visits of EOT, TOC and LFU.

- **Indeterminate**: Either clinical outcome or microbiological outcome, or both, are considered as indeterminate at the visits of EOT, TOC and LFU.

The clinical outcomes recorded in the clinical database and the microbiological outcomes from central laboratory will be used for analyses.

8.2.4.1. By-Subject Overall Outcomes Analysis

The proportions of subjects with overall success at EOT, TOC, and LFU visits will be provided for each treatment group together with the treatment difference and the corresponding CIs in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations.

Treatment differences for overall success will be analyzed in a similar way to the primary efficacy endpoint described in Section 8.1.2.1.

Death will be considered as failure. Subjects with missing or indeterminate clinical or microbiological responses will be considered failures in the analyses in the micro-MITT, extended micro-MITT, and CR-MITT populations.

In addition, the number and proportion of subjects having overall outcome as success, failure and indeterminate will be summarized by treatment group.

Provides a comprehensive list of overall outcomes, organized in ascending order by subject number.

8.2.4.2. By-Subject Overall Outcomes Subgroup Analysis

Overall success rates at EOT, TOC, and LFU visits will be analyzed in the micro-MITT population in subgroups similar to those described in Section 8.1.2.4.

8.2.4.3. By-Pathogen Overall Outcomes Analysis

In the micro-MITT population, provide the proportion of subjects in each treatment group with overall success by gram-negative pathogens on EOT, TOC, and LFU visit.

In addition to the above analyses in the micro-MITT, extended micro-MITT, CR-MITT, and ME populations, the overall success rate at EOT, TOC, and LFU visits for subjects in the corresponding treatment groups will be listed by the species of gram-negative pathogens detected at baseline, and by the MIC values at baseline for IMI-XNW4107 and IMI\REL.

8.3. Exploratory Endpoint

Healthcare utilization of subjects assessed at LFU visit as follows:

- Total number of days spent in hospital post-randomization in the MITT population.
- Total days spent in intensive care unit (ICU) post-randomization in the MITT population.
- Total days spent on mechanical ventilation post-randomization for the subgroup of subjects on mechanical ventilation at enrollment (VABP/ventilated HABP) in the MITT population.

The total number of days after the above randomization is calculated as follows:

- Data from hospitalization/ICU/mechanical ventilation where the date is missing and the status is not sustained will not be included in the calculations.

- The date of the LFU visit was used as the cutoff date for hospitalization/ICU/mechanical ventilation status that was continuous, and the study end date was used as the cutoff date for missing LFU visits.
- The cutoff for hospitalization/ICU/mechanical ventilation was after the LFU visit, with the LFU visit date used for the cutoff (for missing LFU visits, the study end date was used as the cutoff date).
- If time was not missing from the data collection, the total length of each hospital/ICU/mechanical ventilation stay after randomization was calculated in segments (if needed) (in hours) and then summed to calculate the total length of time, which was then converted to the total number of days (divided by 24).
- During the segmentation process, if the start and cut-off times were missing from the data collection, 12:00 of the day was used to fill them in.
- During segmentation, if only the start time is missing from the data collection, use 0:00 of the day to fill in.
- During the segmentation process, if only the cut-off time was missing from the data collection, it was filled in using 23:59 of the day.

Post-randomization periods = Cut-off time - Start time (the later of the filled random time and the corresponding occurrence time)

If there were multiple segments of hospitalization/ICU/mechanical ventilation for the same subject, the results for each segment were summed to calculate the total duration (in hours), which was then converted to the total number of days (divided by 24).

8.3.1. Exploratory Analysis

Descriptive statistics will be provided for the total number of days spent in the hospital/ in the ICU/ on mechanical ventilation from the time of post-randomization for the MITT population. Number of days on mechanical ventilation will be analyzed in the subgroup of ventilated subjects at baseline.

Provides a list of the total number of days in the hospital after randomization, the total number of days in the intensive care unit, and the total number of days on mechanical ventilation after randomization for the subjects, sorted in ascending order by subject number.

8.4. Other Efficacy Endpoints

Other efficacy analysis will be summarized based on the MITT Population.

8.4.1. Chest Imaging

A by-subject listing of chest imaging will be provided by visit in chronological order.

8.4.2. Oxygenation Status

Descriptive statistics will be provided by treatment group for Oxygenation status related test as follows:

- Baseline value
- Values at each postbaseline visit (nominal visit)
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline for a postbaseline visit will be defined as the postbaseline value minus the baseline value. Oxygenation status related test measured at unscheduled visits before first dose will be included for the baseline value selection.

Descriptive analysis of oxygenation status will be performed using the following units: PaO_2 (mmHg), FiO_2 (unitless), O_2 saturation (%), PH (unitless) and PaO_2/FiO_2 (unitless).

A list of subjects' oxygenation status will be provided in chronological order of visit, in ascending order of subject number.

8.4.3. Sequential Organ Failure Assessment (SOFA) score

Descriptive statistics will be provided by treatment group for total SOFA Score as follows:

- Baseline value
- Values at each postbaseline visit (nominal visit)
- Change from baseline at each postbaseline visit

BA baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Total SOFA Score measured at unscheduled visits before first dose will be included for the baseline value selection.

A by-subject listing of SOFA score will be provided by visit in chronological order.

8.4.4. Glasgow Coma Score (GCS)

Descriptive statistics will be provided by treatment group for total Glasgow Coma Score as follows:

- Baseline value
- Values at each postbaseline visit (nominal visit)
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Total Glasgow Coma Score measured at unscheduled visits before first dose will be included for the baseline value selection.

A by-subject listing of Glasgow Coma Scale will be provided by visit in chronological order.

8.4.5. HABP/VABP Clinical Signs/Symptoms

The proportions of subjects with HABP/VABP clinical signs/symptoms assessment at all visits will be provided for each treatment group in the MITT populations.

A by-subject listing of HABP/VABP clinical signs/symptoms will be provided by visit in chronological order.

9. SAFETY ANALYSIS

9.1. Adverse Events and Deaths

9.1.1. Adverse Events Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

9.1.2. Adverse Events Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to terminology criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

9.1.3. Relationship of Adverse Events to Study Drugs

Related AEs are those for which the investigator selected "Definitely related", "Probably related" or "Possibly related" on the AE CRF to the question of "Relationship to study drug". Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

9.1.4. Serious Adverse Event

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol.

9.1.5. Treatment-Emergent Adverse Events

9.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AEs with an onset time at or after the study drug start time.

9.1.5.2. Incomplete Dates

If the date/time of occurrence of the AE was incomplete and the date/time of the end of the AE was not earlier than the date/time of the first administration of the study drug, the date/time of occurrence, month, and year (or month and year only, and so on if the date/time was not documented) were used to determine whether or not the AE was a therapeutic-phase adverse event. The AE was considered a treatment-phase adverse event if both of the following criteria were met:

- Date/time of AE occurrence is the same as or after the month and year (or year) of the date/time of the first dose of study medication

If the onset and end date/time of an AE are missing completely, or if the onset date/time is missing and the end date/time is later than the date of the first dose, then the AE will be considered a therapeutic period adverse event. In addition, an AE will be considered a treatment-period

adverse event if the AE's onset date/time is missing and the end date/time is incomplete but the month and year (or year only if the month is not recorded) are the same as or after the date of the first dose.

9.1.6. Summary of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Population.

9.1.6.1. Summary of Treatment-Emergent Adverse Events Incidence

A summary table of TEAEs by treatment group is given, and the number of cases and percentage of subjects experiencing at least 1 TEAE by SOC, PT, and treatment group will also be summarized for the following classifications:

- TEAE
- Drug-related TEAE
- TEAE with Grade 3 or higher
- Drug-related TEAE with Grade 3 or higher
- Serious TEAE
- Drug-related Serious TEAE
- Drug discontinuation due to TEAE
- Drug discontinuation due to Drug-related TEAE
- Study discontinuation due to TEAE
- Study discontinuation due to Drug-related TEAE
- TEAE with incidence greater than 1% (based on total group)
- Drug-related TEAE with incidence >1% (based on total group)
- TEAE leading to death
- Drug-related TEAE leading to death

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, severity grade and treatment group:

- TEAE
- TEAE with Grade 3 or higher
- Drug-related TEAE
- Drug-related TEAE with Grade 3 or higher
- Serious TEAE
- Drug-related Serious TEAE

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in descending order of the XNW4107 group frequency within each SOC and PT, if SOC or PT frequency are same, alphabetic order will be used within each SOC or PT.

For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition, data listings will be provided for the following:

- All AEs, labeled as TEAE or not
- TEAE with Grade 3 or higher
- Serious TEAE
- Drug interruption due to TEAE
- Drug discontinuation due to TEAE
- Study discontinuation due to TEAE
- AE leading to death

9.1.6.2. Subgroup analysis of treatment-emergent adverse events

The incidence of TEAE and deaths mentioned in Section 9.1.6.1 will be summarized in the safety population in a manner similar to that described in Section 8.1.2.4 and analyzed by the following subgroups.

- Age (< 65 years and≥ 65 years)
- Gender (male and female)
- Region (China and the rest of the world)
- Type of infection at baseline (non-ventilated HABP and ventilated HABP)
- Baseline APACHE II total score (<15 and≥ 15)
- Baseline eGRF (<30 mL/min, 30 to <60 mL/min, 60 to <90 mL/min, 90 to <150 mL/min, 150 to< 250 mL/min and ≥250 mL/min)
- Baseline liver function (abnormal and normal)

9.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Population and will include data collected though out the study. The analysis will be based on values reported in system international units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.6.

Laboratory evaluations will be summarized based on the safety population.

A by-subject listing for laboratory test results will be provided by visit in chronological order for hematology, biochemistry, coagulation and urinalysis separately.

9.2.1. Summary of Numerical Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory test as follows:

- Baseline value
- Values at each post-baseline visit (nominal visit)
- Change from baseline at each post-baseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. Laboratory test results measured at the unplanned visit prior to the first dose of medication will be included in the selection of the baseline value.

9.2.2. Shifts Relative to the Baseline Values

A shift table of the investigators' assessment of laboratory results at each visit (nominal visit) compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

9.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have no missing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

9.3. Vital Signs

Vital signs will be summarized based on the Safety Population.

Descriptive statistics will be provided by treatment group for vital signs as follows:

- Baseline value
- Values at each post-baseline visit (nominal visit)
- Change from baseline at each post-baseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline for a postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits before first dose will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.5.

A by-subject listing of vital signs will be provided by visit in chronological order.

9.4. Electrocardiogram Results

Electrocardiogram (ECG) analysis results are intended to identify meaningful changes in the QT interval. If potential abnormalities of interest are identified, further analyses may be conducted. Summaries of investigator assessment of ECG readings will be provided for the Safety Population for each scheduled time point.

9.4.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each visit (nominal visit) compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

A by-subject listing for ECG assessment results will be provided visit in chronological order.

9.4.2. Corrected QT interval

The QT interval (measured in milliseconds) is the time between the beginning of the Q wave and the end of the T wave in the cardiac cycle. The QT interval represents the process of electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been developed to correct the QT interval using heart rate.

The QT (QTc) interval (QTcF), corrected using the Fridericia method, is as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in milliseconds; RR = 60/heart rate (beats/minute) and RR is measured in seconds.

The maximum post dose change in QTcF interval values obtained during the study will be summarized within the following categories:

- Maximum QTcF≤ 450 ms and change from baseline > 30 ms
- Maximum QTcF≤ 450 ms and change from baseline > 60 ms
- Maximum QTcF> 450 ms and change from baseline > 30 ms
- Maximum QTcF > 450 ms and change from baseline > 60 ms
- Maximum QTcF > 480 ms and change from baseline > 30 ms
- Maximum QTcF > 480 ms and change from baseline > 60 ms
- Maximum QTcF > 500 ms and change from baseline > 30 ms
- Maximum QTcF > 500 ms and change from baseline > 60 ms

The QTcF interval and uncorrected QT interval results and their change relative to baseline at each visit (nominal visit) will be summarized by treatment group, using descriptive statistics. ECG results measured at the unplanned visit before the first dose of medication will be included in the selection of baseline values.

9.5. Physical Examination

A shift table of the physical examination results at each visit (nominal visit) compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

A by-subject listing of physical examination will be provided by visit in chronological order.

10. PHARMACOKINETIC (PK) ANALYSIS

10.1. Pharmacokinetic Sample Collection

XNW4107-302 Blood samples for XNW4107, imipenem, and cilastatin plasma drug concentrations were collected prior to administration on Day 4 (+2 days), 5-25 min and 2-3 hours after completion of the 30-min intravenous infusion on that day. These samples may be collected at the time of any of the 4 infusions on Day 4 (+2 days).

10.2. Pharmacokinetic Analysis

Pharmacokinetic analysis will be summarized based on the pharmacokinetic population.

Concentration time data for XNW4107, imipenem, and cilastatin will be analyzed and summarized using descriptive statistics (number of subjects, arithmetic mean, geometric mean, median, first quartile, third quartile, standard deviation, minimum, maximum, coefficient of variation, and geometric coefficient of variation) for each of the specified sampling time windows.

In the summary statistics, the BLQ values at all time points are considered to be zero.

Concentration-time data at each scheduled collection timepoint will be displayed graphically on the linear and semi-logarithmic scales as mean + standard deviation.

A by-subject listing of PK sampling details will be provided by visit in chronological order.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

Subjects will be randomly assigned to treatment groups in a 1:1 ratio (Protocol V1.0) and a 2:1 ratio (Protocol V3.3 and beyond) using stratified randomization via interactive voice or web-based response systems (IRT). In the final analysis, the data will contain subjects enrolled in both randomized ratios.

In the protocol, for the primary efficacy endpoint, the randomization stratification factor-corrected Mantel-Haenszel stratification method (Koch, 1989) will be used to provide the difference in proportions between groups (i.e., rate difference: IMI-XNW4107 group minus IMI/REL group) and their 95% two-sided CIs. However, due to the number of subjects actually enrolled in other countries and regions outside of China was very small, in Section 8.1.2.1, country/region (China vs. other countries and regions) in the randomization stratification factor was excluded from the analysis, and treatment comparisons were made by the following stratification factor (IMI XNW4107 group minus IMI/REL group):

- Type of infection (non-ventilated HABP vs. ventilated HABP).
- APACHE II scores (<15 versus ≥15).

New extended micro-MITT 2 analysis population and addition of microbial efficacy by subject and microbial efficacy by pathogen in the extended micro-MITT 2 population.

For imputation rules of all-cause mortality (except for sensitivity analyses), subjects with unknown survival status at Day 14 and Day 28 will not be considered deaths in either treatment group.

12. REFERENCES

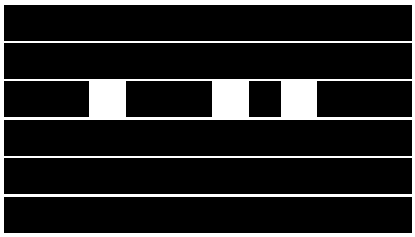
Koch GG, Carr GJ, Amara IA, et al. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989: pp. 414-421

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc, 1987

13. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

14. SAP VERSION REVISIONS

Revision date	Section	Summary of Revisions	Reason for Revision
June 25, 2025	Department of Biostatistics	1. Update abbreviations. 2. Revise descriptions in the Microbiology Data section. 3. For all-cause mortality imputation (excluding sensitivity analyses), Subjects with unknown survival status at Day 14/Day 28 shall not be considered deaths in either treatment group. Survival analysis has been added. 4. Any pathogen detected in blood culture samples is defined as bacteremia. 5. For pathogens missing IMI/REL susceptibility data, impute using IMI susceptibility results. 6. In primary Estimand, APACHE II score is used as a continuous variable in the sensitivity analysis.	1. Added new abbreviations. 2. Added detailed descriptions. 3.  subjects with missing survival status will not be considered deaths. Results of the survival analysis were also supplemented. 4. The definition of bacteremia was updated based on expert judgment. 5. The mechanism of action of imipenem/relebactam (IMI/REL) is that relebactam inhibits bacterial β-lactamases, thereby restoring activity against imipenem-resistant pathogens. For pathogens inherently susceptible to imipenem, relebactam is not required. Therefore, for imipenem-susceptible pathogens missing IMI/REL susceptibility data, susceptibility to IMI/REL shall be imputed as susceptible (S). 6. All-cause mortality in the trial was low, and some strata at randomization contained no deceased subjects; these data could not be used for imputation.