- TITLE PAGE

Protocol

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

Study Alias: REITAB-2

[redacted]

Investigational Medicinal Product:

Imipenem/Cilastatin in Combination with XNW4107 for Injection

Protocol Reference Number: XNW4107-302
EUCTR Number: 2022-501952-27-00
NCT number: NCT05204563
IND Number: 146614

Sponsor:
[redacted]

SPONSOR APPROVAL

I have read the following and approve it:

[redacted]

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

[Name, Qualification(s)] Principal investigator	Date

SYNOPSIS

Title of study: 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

Indication: Hospital-acquired bacterial pneumonia (HABP), including ventilated HABP (vHABP) and ventilator-associated bacterial pneumonia (VABP) caused by Gram-negative bacteria.

Number of investigators and study centers:

[redacted]

Development phase: Phase 3

Objectives:

Primary objective

To evaluate the all-cause mortality rate through Day 14 [redacted] group in the Modified Intent-to-Treat (MITT) population.

Secondary objectives

The secondary objectives of this study are:

Efficacy

- To evaluate the all-cause mortality rate through Day 28 [redacted] in the MITT population
- To evaluate the all-cause mortality rate through Day 14 and through Day 28 [redacted] in the Microbiologic MITT (micro-MITT), extended micro-MITT, clinically evaluable (CE), microbiologically evaluable (ME) and Carbapenem-resistant MITT (CR-MITT) populations
- To evaluate the clinical outcome of [redacted], 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 [redacted] 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 [redacted] at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations

[redacted]

Safety

To evaluate the safety and tolerability of [redacted]

[redacted] in subjects with HABP or VABP in the Safety population (SAF).

Pharmacokinetics

[redacted]

Exploratory objective

Healthcare Utilization

To determine the healthcare utilization[redacted] in the MITT population.

Methodology/study design:

This study 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 subjects with HABP/VABP caused by Gram-negative bacteria.

Approximately [redacted] 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). [redacted]

Subjects will be randomly assigned to study treatment in a double blind- manner [redacted] via an Interactive Web/Voice Response System to receive either imipenem 500 mg/cilastatin 500 mg-XNW4107 250 mg (N=300) infused IV as a 30-minute infusion (±5 minutes) every 6 hours ±30 minutes (q6h ±30 minutes) or IMI/REL 1.25 g IV (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) ([redacted]) 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 as judged by the investigator can be given to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) as per the local standard of care. The treatment duration for 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 a LFU visit (Day 28 [±3 days]).

An independent Data Monitoring Committee (DMC) will be employed to oversee the progress of this study and to ensure the ongoing safety of 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.

An independent Data Review Committee (DRC), which will be separated from the DMC, will be employed to perform the sample size re-estimation. [redacted]

Number of subjects:

It is anticipated that approximately [redacted] will be enrolled and randomized into the study in [redacted]

Diagnosis and main criteria for inclusion and exclusion:

Subjects must meet the following inclusion criteria to be eligible for the study:

1. Subjects willing and able to provide written informed consent or where consent is provided by legally authorized representatives.
2. Willing and able to comply with all study assessments and adhere to the protocol schedule.
3. Male or female subjects ≥18 years on the day of signing informed consent.
4. Has HABP or VABP as defined below and requires treatment with IV antibiotic therapy.
   NOTE: HABP is defined as the onset of acute bacterial pneumonia symptoms at least 48 hours after hospitalization or within 7 days after discharge from an inpatient acute or chronic care facility (e.g., long-term care, rehabilitation center, hospital, or skilled nursing home).
   Subjects may experience acute respiratory failure and require mechanical ventilation for HABP (vHABP).
   VABP is defined as acute bacterial pneumonia in a subject receiving mechanical ventilation via an endotracheal (or nasotracheal) tube or tracheostomy for ≥48 hours.
5. All subjects must fulfill at least 1 of the following clinical criteria at screening:
   a. New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (e.g., respiratory rate >25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation [redacted]
   c. Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure
   d. New onset of or increase in (characteristics or quantity) suctioned respiratory secretions, [redacted]
6. All subjects must have at least 1 of the following signs and symptoms/laboratory abnormalities at screening:
   a. Documented fever (i.e., [redacted]
   b. Hypothermia [redacted]
   c. Leukocytosis with a total peripheral white blood cell (WBC) count ≥10,000 cells/mm^3

d. Leukopenia with total peripheral WBC count ≤4500 cells/mm^3
e. Greater than 15% immature neutrophils (bands) noted on peripheral blood smear.

7. All subjects must have a chest radiograph during screening or have a previous chest radiograph within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. A computed tomography scan in the same time window showing the same findings could also be acceptable.
8. All subjects must have a suspected Gram-negative infection involving the lower respiratory tract by [redacted]
9. Agree to allow any bacterial isolates obtained from protocol-required specimens related to the current infection to be provided to the Central Microbiology Reference Laboratory for study-related microbiological testing, long-term storage, and other future testing.
10. Female subjects of childbearing potential, who are willing to use a highly effective method of birth control during the study and for at least 30 days following the last dose of study medication.
    a. Childbearing potential is defined as any female who has experienced menarche and does not meet the criteria for postmenopausal, which is defined as the past 12 months with no menses without an alternative medical cause or permanently sterilized (e.g., has undergone bilateral tubal occlusion/ligation, hysterectomy, bilateral oophorectomy, bilateral salpingectomy)
    b. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or a vasectomized partner (see also Section 6.2).
11. Male subjects with female sexual partners of childbearing potential are eligible for inclusion if they agree to use medically acceptable birth control for 90 days following the last dose of study medication. Sexual abstinence, vasectomy, or a condom used with a spermicide are medically acceptable birth control methods for males. Male subjects must agree not to donate sperm for a period of 90 days after the last dose of study treatment.

Subjects who meet any of the following exclusion criteria are not eligible to participate in the study:

1. If a Gram stain from a respiratory sample is available and shows only Gram-positive cocci.
2. Subjects who have known or suspected community-acquired bacterial pneumonia, atypical

pneumonia, viral pneumonia including Coronavirus disease (COVID-19), or chemical pneumonia (including aspiration of gastric contents, inhalation injury).

3. Subjects who have HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.
4. Have received effective systemic and inhaled Gram-negative antibacterial drug therapy for the index infection of HABP/VABP for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization.
   [redacted].
5. Has a concurrent condition or infection that, in the investigator's judgment, would preclude evaluation of therapeutic response (e.g., active tuberculosis, cystic fibrosis, granulomatous disease, a disseminated fungal infection, invasive fungal pulmonary infection, or endocarditis).
6. Subjects who have central nervous system infection (e.g., meningitis, brain abscess, shunt infection).
7. Documented presence of immunodeficiency or an immunocompromised condition including hematologic malignancy, bone marrow transplant, known history of human immunodeficiency virus infection with a CD4 count <200/mm^3, or requiring frequent or prolonged use of systemic corticosteroids (≥20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions).
8. Documented hypersensitivity to any carbapenem antibacterial agent or documented severe hypersensitivity to any other type of β-lactam antibacterial agent, or previous severe adverse drug reaction to any β-lactam antibiotics, or any of the excipients used in the study drug formulations.
9. History of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years).
10. Renal function at screening as estimated glomerular filtration rate (eGFR) <15 mL/min or > 250 mL/min, calculated as individual eGFR derived from Modification of Diet in Renal Disease formula.
11. Subject is receiving hemodialysis or peritoneal dialysis or micro-dialysis or continuous venovenous hemofiltration or continuous venovenous hemodialysis.
12. Subject is anticipated to be treated with any of the following medications during the course of study therapy:
    a. Valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening)
       [redacted]
    b. Concomitant systemic (IV or oral) Gram-negative antibacterial agents in addition to those designated in the study treatment groups
    c. Concomitant systemic (IV or oral) antifungal or antiviral therapy for the index

infection of HABP/VABP.

13. Life expectancy is <3 days.
14. Subjects in refractory septic shock, defined as persistent hypotension despite adequate fluid resuscitation and vasopressive therapy at the time of randomization.
15. Subjects with 1 or more of the following laboratory abnormalities in baseline specimens: aspartate aminotransferase, alanine aminotransferase >3 × the upper limit of normal (ULN), total bilirubin level >2 × ULN (except for isolated hyperbilirubinemia due to known Gilbert's disease), neutrophils <500 cells/mm^3, platelet count <40,000/mm^3.
16. History of active liver disease or cirrhosis.
17. Subjects with an APACHE II score of >30.
18. A female who is pregnant or breastfeeding or has a positive pregnancy test at screening.
19. Subject is participating in any clinical study of any investigational medication (i.e., non-licensed medication) during the 30 days prior to randomization. COVID-19 vaccines that are given under emergency use authorization are not considered investigational agents.
20. Any other condition or prior therapy, which, in the opinion of the investigator, would make the subject unsuitable for this study.

Test products, dose, and mode of administration:

All study drugs will be administered in a double-blind manner. The test and the comparator drugs will be provided by the sponsor to the site.

[redacted]

Reference therapy, dose, and mode of administration:

[redacted]

Blinding:

All study personnel and subjects will be blinded to the treatment assignment with the exception of the specific personnel as described in Section 5.10 and in a separate Maintaining Study Blind and Unblinding Plan.

Duration of subject participation in the study:

Planned screening duration: up to 24 hours

Planned treatment duration: 7 to 14 calendar days

Planned follow-up duration: 14 to 21 calendar days

Total duration of study participation: up to 32 calendar days.

Study populations:

Intent-to-Treat (ITT) population: All subjects who are randomized. Subjects are analyzed according to the randomized treatment, regardless of the treatment actually received.

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.

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.

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.

Pharmacokinetic (PK) population: All subjects from the SAF with at least 1 reportable concentration of XNW4107, imipenem, or cilastatin.

Evaluation: Efficacy

Primary efficacy endpoint:

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

Secondary efficacy endpoints:

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.

Exploratory endpoints:

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/vHABP) in the MITT population.

[redacted]

Evaluation: Safety

The safety and tolerability endpoints will be evaluated by the following measures in the SAF:

- Incidence of all adverse events (AEs), treatment-emergent AEs (TEAEs), including serious AEs

(SAEs)

- 12-lead electrocardiogram (ECG)
- Vital sign measurements including body temperature, blood pressure, heart rate, and respiratory rate
- Clinical laboratory tests including serum chemistry, hematology, urinalysis, and coagulation

Physical examination findings.

Evaluation: Pharmacokinetics

Blood samples for quantification of XNW4107, imipenem, and cilastatin concentration levels will be collected on Day 4 (+2 days) at pre-dose, 5 to 25 minutes, and 2 to 3 hours after completion of one of that day's 30-minute IV infusions for descriptive summary and plotting of XNW4107, imipenem, and cilastatin plasma concentrations.

[redacted]

General Considerations for Data Analyses

Complete details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan. Statistical analysis will be performed using SAS System, version 9.4 or higher (SAS Institute, Inc., Cary, NC).

Efficacy Analysis

Estimand for the Primary Endpoint

[redacted]

[redacted]

- [redacted].

Primary Efficacy Analysis

[redacted].

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.

[redacted].

Secondary Efficacy Analysis

The secondary efficacy endpoint, the all-cause mortality rate through Day 28 will be analyzed for the MITT population using the same method described for the primary analysis.

[redacted]

Exploratory Analysis

For exploratory analysis, descriptive statistics will be provided for total number of days spent in the

hospital/ in the ICU/ on mechanical ventilation from time of randomization for the MITT population. Number of days on mechanical ventilation will be analyzed in the subgroup of ventilated subjects.

Safety and Tolerability Analysis

Safety and tolerability will be evaluated by presenting summaries of TEAEs, routine clinical laboratory evaluations, ECGs, vital signs, and physical examination findings for each treatment group and overall.

All safety and tolerability analyses will be performed using the SAF.

All analyses of safety and tolerability endpoints will be descriptive only, and no inferential statistics will be provided.

PK Analysis

Concentration-time data for XNW4107, imipenem, and cilastatin will be analyzed and summarized by analyte using descriptive statistics (number of subjects, arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) at each scheduled collection time interval. Concentration-time data will be displayed graphically on the linear and semi-logarithmic scales.

[redacted].

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LIST OF ABBREVIATIONS

Abbreviation	Definition
β-hCG	beta-human chorionic gonadotropin
ABG	arterial blood gas
AE	adverse event
ALT	alanine transaminase
AM	alveolar macrophage
AmpC	ampicillin C
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-6h}	area under the plasma concentration-time curve from time 0 to 6 hours post-dose
AUC_{0-24h}	area under the plasma concentration-time curve from time 0 to 24 hours post-dose
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{ss}	area under the concentration-time curve at steady state
BAL	bronchoalveolar lavage
BID	twice daily
BP	blood pressure
BSA	body surface area
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CFU	colony forming unit
CI	confidence interval
CL	clearance
CL_R	renal clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady state
CNS	central nervous system
COVID-19	coronavirus disease
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-resistant *Enterobacterales*
CR-MITT	Carbapenem-resistant MITT
CRPA	Carbapenem-resistant *Pseudomonas aeruginosa*
CSA	clinical study agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTX-M	Cefotaximase-Munich
CYP	cytochrome P450
DMC	Data Monitoring Committee
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtrate rate
ELF	epithelial lining fluid

Abbreviation	Definition
EOS	end of study
EOT	end of treatment
ESBL	extended-spectrum beta-lactamase
FDA	Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HABP	hospital-acquired bacterial pneumonia
hERG	human ether-à-go-go-related gene
HR	heart rate
HSR	human-simulated regimen
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IMI/REL	imipenem/cilastatin/relebactam
IMP	investigational medicinal product
IRB	institutional review board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
IXRS	Interactive Web/Voice Response System
KPC	Klebsiella *pneumoniae carbapenemase*
LFU	Late Follow-up
MATE	multi-drug and toxin extrusion
MDR	multi-drug resistance
MDRD	Modification of Diet in Renal Disease
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-MITT	Microbiologic Modified Intent-to-Treat
MITT	Modified Intent-To-Treat
NMPA	National Medical Products Adminstration
MRSA	methicillin-resistant *Staphylococcus aureus*
NOAEL	no observable adverse effect level
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OXA	oxacillinase
PaO_2	partial pressure of oxygen
PBS	protected brush specimen
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PT	preferred term
PTA	PK/PD target attainment

Abbreviation	Definition
q6h	every 6 hours
RBC	red blood cell
RI	renal impairment
RR	respiratory rate
SAE	serious adverse event
SAF	Safety population
SBECD	sulfobutyl-ether-β-cyclodextrin
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia
V_{ss}	apparent volume of distribution at steady state
WBC	white blood cell

1. INTRODUCTION

1.1. Study Rationale

Evopoint Biosciences USA, Inc. (hereafter referred as Evopoint), formerly known as Sinovent Pharmaceuticals, Inc. (Sinovent), intends to develop XNW4107, a novel β-lactamase inhibitor, in combination with imipenem/cilastatin, a β-lactam antibiotic, for intravenous (IV) administration to combat severe Gram-negative bacterial infections. This combination of imipenem/cilastatin and XNW4107 (from hereon will be referred to as IMI-XNW4107, or investigational medicinal product [IMP]) is being developed for subjects 18 years of age and older for the following indications in their clinical development program: complicated urinary tract infection including acute pyelonephritis, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) which represent diseases with an alarming increase in the incidence of β-lactamase-producing organisms.

This strategy of combining a β-lactam antibiotic and β-lactamase inhibitor for the treatment of infections caused by β-lactamases-producing pathogens has been successful in the treatment of a variety of bacterial infections. Gram-negative pathogens, including those producing extended-spectrum β-lactamases (ESBLs) and carbapenemases, are important causes of nosocomial infections. The combination of IMI-XNW4107 is potentially capable of providing an effective therapy covering the pathogens commonly responsible for HABP/VABP.

This is a Phase 3 study to evaluate the efficacy and safety of IMI-XNW4107 with the intention to demonstrate that IMI-XNW4107 is non-inferior to imipenem/cilastatin/relebactam (referred to as IMI/REL) in the treatment of adult subjects diagnosed with HABP/VABP.

1.2. Background

1.2.1. Disease Information

HABP/VABP by definition occurs in hospitalized subjects with a hospital stay of 48 hours or more. According to the FDA Guidance for Industry in 2020 (FDA, 2020), clinical signs and symptoms of HABP include fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a subject hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital. Clinical signs and symptoms of VABP include fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a subject receiving mechanical ventilation via an endotracheal (or nasotracheal) tube for a minimum of 48 hours. Gram-negative bacilli, including *Enterobacteriaceae*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Acinetobacter baumannii* (*A. baumannii)* are among the most common etiologic pathogens for HABP/VABP (Jones RN, 2010; Sader HS, 2014), and treatment with HABP/VABP are complicated by the increasing prevalence of ESBL-producing pathogens.

Multi-drug resistance (MDR) in HABP/VABP infections, particularly carbapenem resistance, has been an increasing global concern, since carbapenems are often the last resort of antibacterial drugs for serious infections caused by multi-drug resistant Gram-negative organisms.

There is a high unmet medical need for new treatment of nosocomial infections such as HABP/VABP. Based on the demonstrated pre-clinical in vitro and in vivo antimicrobial profiles of XNW4107 to restore the antimicrobial activity of imipenem-resistant pathogens including carbapenem-resistant *Enterobacterales* (CRE), MDR of *P. aeruginosa*, and *A. baumannii*, and the safety and pharmacokinetic (PK) data from the Phase 1 studies, XNW4107 in combination with imipenem/cilastatin carries broad spectrum of Gram-negative activity for the treatment of subjects with HABP/VABP being studied in this trial.

1.2.2. XNW4107 for Injection

[redacted]

[redacted]

XNW4107 is being developed to restore the activity of imipenem in carbapenem-resistant Gram-negative bacterial infections.

Imipenem/cilastatin is a combination of imipenem, a carbapenem antibacterial drug, and cilastatin, a renal dehydropeptidase inhibitor that limits the renal metabolism of imipenem. Imipenem was approved in the US in 1985 and is approved for several indications, including urinary tract, intra-abdominal, and lower respiratory tract infections, with well-established records of safety and effectiveness for clinical use.

[redacted]

1.2.3. Non-Clinical Experience

Data as summarized in the XNW4107 investigator brochure (IB) are provided; for details, refer to the XNW4107 IB.

1.2.3.1. Primary and Secondary Pharmacology

[redacted]

[redacted]

[redacted]

1.2.3.2. Safety Pharmacology

An in vitro tail current assay in human ether-à-go-go-related gene (hERG)-transfected HEK-293 cells showed that XNW4107 at 225 μM had a minor inhibitory effect on hERG potassium channel currents. The vehicle corrected inhibition of the current at a nominal concentration of 225 μM for XNW4107 equaled to 12.0 ±1.4%. The half-maximal inhibitory concentration value was not determined and considered to be >225 μM, which is unlikely to be of clinical significance. The effects of XNW4107 on the cardiovascular system in conscious telemetered male Beagle dogs were also evaluated. A transient decrease in PR interval duration and body temperature were observed from 10 minutes to 1 hour and 1 to 4 hours after administration of 200 mg/kg of XNW4107 (which is equivalent to 7778 mg in 70 kg humans).

The respiratory effects of XNW4107 were examined in the conscious male Sprague-Dawley rats following the infusion of XNW4107 at 0, 50, 150, or 300 mg/kg dose levels. Based on the results evaluated by whole-body plethysmography, ≤300 mg/kg of XNW4107 did not affect any of the respiratory parameters (including tidal volume, respiratory rate, and minute volume) when compared to baseline values.

[redacted] No other relevant XNW4107-related effects were noted for any of the parameters evaluated or at any dose tested.

1.2.3.3. Pharmacokinetics and Metabolism

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] No appreciated accumulation of XNW4107 was observed in any of the tested species. Both XNW4107 and imipenem can penetrate into the lungs as demonstrated concentration levels at BAL in mice.

1.2.3.4. Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

1.2.4. Clinical Experience

[redacted]: [redacted] The data provided are as summarized in current investigator's brochure (IB) (XNW4107 IB); for details, refer to the XNW4107 IB.

Table 1: [redacted]

[redacted]

1.2.4.1. Summary of Pharmacokinetics and Drug Metabolism

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

1.2.4.2. *Safety*

The 5 Phase 1 studies conducted in healthy subjects or subjects with RI have demonstrated a good safety profile with XNW4107 administered alone or in combination with imipenem/cilastatin as a single dose or multiple repeated doses.

[redacted]

[redacted]

1.3. Benefit-Risk Assessment

The study may provide individual and general benefits.

The population for this study consists of subjects with HABP/VABP with serious infections requiring IV antibiotics where limited therapeutics options remain despite the availability of recent agents to treat these infections.

There is a potential benefit to the subjects participating in this study to receive effective antibacterial treatment, including infections with resistant Gram-negative pathogens.

In general, the study has the potential benefit to identify a new antibacterial combination for the treatment of HABP/VABP in the face of emerging antibacterial resistance and the need for new antibacterial agents.

[redacted].

The risks for imipenem/cilastatin are well known and widely available in their respective Prescribing Information or Summary of Product Characteristic (SmPC). The most frequently occurring adverse reactions (≥0.2%) in adults were phlebitis, nausea, diarrhea, vomiting, rash, pain at injection site, fever, hypotension, seizures, erythema at injection site, dizziness, pruritus, vein induration, urticaria, and somnolence (Imipenem/Cilastatin [Package Insert], 2022). Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in subjects receiving therapy with β-lactams; these reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens (Imipenem/Cilastatin [Package Insert], 2022). Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with imipenem/cilastatin, especially when recommended dosages were exceeded. These experiences have occurred most commonly in subjects with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function (Imipenem/Cilastatin [Package Insert], 2022). Dosage adjustment is necessary for subjects with RI (Imipenem/Cilastatin [Package Insert], 2022). Adult subjects with CL_{CR} ≤20 mL/min, whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines and regular monitoring of CL_{CR} for these subjects is recommended. [redacted]

[redacted]

Imipenem/cilastatin/relebactam is approved for the treatment of Gram-negative infections including HAPB/VABP in many countries and has a safety profile consistent with imipenem/cilastatin. Detailed information on the safety and risk profile of IMI/REL is provided in the Package Insert and SmPC.

Coronavirus Disease (COVID-19) Pandemic

The safety monitoring and risk mitigations defined in this study protocol and related study documents have taken into consideration the additional potential impacts of the COVID-19 pandemic if still active during the conduct of this study.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

To evaluate the all-cause mortality rate through Day 14 [redacted] the Modified Intent-to-Treat (MITT) population.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

Efficacy

- To evaluate the all-cause mortality rate through Day 28 p[redacted] in the MITT population
- To evaluate the all-cause mortality rate through Day 14 and through Day 28 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] at EOT, TOC, and LFU visits in the micro-MITT, extended micro-MITT, ME, and CR-MITT populations

[redacted]

Safety

To evaluate the safety and tolerability of I[redacted] subjects with HABP or VABP in the Safety population (SAF).

Pharmacokinetics

[redacted]

2.1.3. Exploratory Objective

Healthcare Utilization

To determine healthcare utilization up to [redacted] group compared to the IMI/REL group in the MITT population.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

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

2.2.2. Secondary Efficacy Endpoints

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 proportion 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.

2.2.3. Secondary Safety Endpoints

The safety and tolerability endpoints will be evaluated by the following measures in the SAF:

- Incidence of all AEs, TEAEs, including SAEs
- 12-lead electrocardiogram (ECG)
- Vital sign measurements including body temperature, blood pressure (BP), heart rate (HR), and respiratory rate (RR)

- Clinical laboratory tests including serum chemistry, hematology, urinalysis, and coagulation
- Physical examination findings.

2.2.4. Pharmacokinetic Endpoint

[redacted]

2.2.5. Exploratory Endpoints

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.

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

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.

The study will be conducted at approximately [redacted] study centers globally.

Approximately [redacted] 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.

[redacted]

Subjects will be randomly assigned to study treatment in a double-blind manner in a [redacted] ratio via an Interactive Web/Voice Response System (IXRS) to receive either imipenem 500 mg/cilastatin 500 mg-XNW4107 250 mg ([redacted]) 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) ([redacted] 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 presents an overview of the study design.

Figure 1: Study Design

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be employed to oversee the progress of this study and to ensure the ongoing safety of 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.

[redacted]

Data Review Committee

[redacted]

[redacted]

3.2. Discussion of Study Design, Including the Choice of Control Groups

Study population: Based on the bacterial etiologic pathogens in HABP and VABP, the spectrum of activity of the combination of IMI-XNW4107, and route of administration, the population targeted for this trial includes subjects with HABP or VABP.

Study design: The overall study design and primary endpoint, the all-cause mortality rate through Day 14 post-randomization in the MITT population, follows the FDA Guidance for the Industry (FDA, 2020), the EMA guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections (EMA, 2018), the Chinese technical guidelines for clinical trials of antimicrobial drugs for HABP/VABP (CDE, 2020), and similar antibacterial clinical development programs for this indication.

[redacted]

Control group (IMI/REL): Based on the spectrum of β-lactamase inhibition to Ambler class A, C, and D, the combination of IMI-XNW4107 is targeting treatment of infections due to Gram-negative pathogens, including isolates resistant to carbapenems. IMI/REL has been selected as the comparator because of its demonstrated efficacy in subjects with HABP/VABP and due to

its microbiological activity against Gram-negative organisms, including carbapenem-resistant pathogens; therefore, allowing the enrollment of all HABP/VABP subjects, including infections due to carbapenem-resistant pathogens.

IMI/REL has been approved in many countries due to its demonstrated efficacy and safety. For countries in which IMI/REL is not yet approved, the Package Insert and SmPC are provided as reference.

The goal of the Sponsor is to bring additional treatment option to the subjects as quick as possible especially for subjects with HABP/VABP that could have *A. baumannii* with etiologic pathogens of up to 25.6% (Yin, 2021), for which the treatment options are limited.

3.3. End of Study Definition

The end of the study (EOS) is defined as the date of the last visit of the last subject in the study.

3.4. Selection of Doses in the Study

[redacted]

[redacted]

4. SELECTION OF STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Subjects ≥18 years of age with a clinical diagnosis of HABP or VABP and requiring treatment with IV antibiotic therapy and have a suspected Gram-negative infection involving the lower respiratory tract.

4.1. Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for the study:

1. Subjects willing and able to provide written informed consent or where consent is provided by legally authorized representatives.
2. Willing and able to comply with all study assessments and adhere to the protocol schedule.
3. Male or female subjects ≥18 years on the day of signing informed consent.
4. Has HABP or VABP, as defined below and requires treatment with IV antibiotic therapy.
   Note: HABP is defined as the onset of acute bacterial pneumonia symptoms at least 48 hours after hospitalization or within 7 days after discharge from an inpatient acute or chronic care facility (e.g., long-term care, rehabilitation center, hospital, or skilled nursing home). Subjects may experience acute respiratory failure and require mechanical ventilation for HABP (vHABP).
   VABP is defined as acute bacterial pneumonia in a subject receiving mechanical ventilation via an endotracheal (or nasotracheal) tube or tracheostomy for ≥48 hours.
5. All subjects must fulfill at least 1 of the following clinical criteria at screening:
   a. New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (e.g., RR >25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation
   b. Hypoxemia [redacted]
   c. Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure
   d. New onset of or increase in (characteristics or quantity) suctioned respiratory secretions, [redacted].
6. All subjects must have at least 1 of the following signs and symptoms/laboratory abnormalities at screening:
   a. Documented fever [redacted]
   b. Hypothermia [redacted]

c. Leukocytosis with a total peripheral white blood cell (WBC) count ≥10,000 cells/mm^3
d. Leukopenia with total peripheral WBC count ≤4500 cells/mm^3
e. Greater than 15% immature neutrophils (bands) noted on peripheral blood smear.

7. All subjects must have a chest radiograph during screening or have a previous chest radiograph within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. A computed tomography scan in the same time window showing the same findings could also be acceptable.
8. All subjects must have a suspected Gram-negative infection involving the lower respiratory tract by [redacted]
9. Agree to allow any bacterial isolates obtained from protocol-required specimens related to the current infection to be provided to the Central Microbiology Reference Laboratory for study-related microbiological testing, long-term storage, and other future testing.
10. Female subjects of childbearing potential, who are willing to use a highly effective method of birth control during the study and for at least 30 days following the last dose of study medication.
    a. Childbearing potential is defined as any female who has experienced menarche and does not meet the criteria for postmenopausal, which is defined as the past 12 months with no menses without an alternative medical cause or permanently sterilized (e.g., has undergone bilateral tubal occlusion/ligation, hysterectomy, bilateral oophorectomy, bilateral salpingectomy)
    b. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or a vasectomized partner (see also Section 6.2).
11. Male subjects with female sexual partners of childbearing potential are eligible for inclusion if they agree to use medically acceptable birth control for 90 days following the last dose of study medication. Sexual abstinence, vasectomy, or a condom used with a spermicide are medically acceptable birth control methods for males. Male subjects must agree not to donate sperm for a period of 90 days after the last dose of study treatment.

4.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible to participate in the study:

1. If a Gram stain from a respiratory sample is available and sample shows only Gram-positive cocci.
2. Subjects who have known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia including COVID-19, or chemical pneumonia (including aspiration of gastric contents, inhalation injury).
3. Subject who has HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.
4. Have received effective systemic and inhaled Gram-negative antibacterial drug therapy for the index infection of HABP/VABP for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization.
[redacted]
5. Has a concurrent condition or infection that, in the investigator's judgment, would preclude evaluation of therapeutic response (e.g., active tuberculosis, cystic fibrosis, granulomatous disease, a disseminated fungal infection, invasive fungal pulmonary infection, or endocarditis).
6. Subjects who have central nervous system infection (e.g., meningitis, brain abscess, shunt infection).
7. Documented presence of immunodeficiency or an immunocompromised condition including hematologic malignancy, bone marrow transplant, known history of human immunodeficiency virus infection with a CD4 count <200/mm^3, or requiring frequent or prolonged use of systemic corticosteroids (≥20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions).
8. Documented hypersensitivity to any carbapenem antibacterial agent or documented severe hypersensitivity to any other type of beta-lactam antibacterial agent, or previous severe adverse drug reaction to any β-lactam antibiotics, or any of the excipients used in the study drug formulations.
9. History of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years).
10. Renal function at screening as estimated eGFR <15 mL/min or ＞250 mL/min, calculated as individual eGFR derived from Modification of Diet in Renal Disease formula.
11. Subject is receiving hemodialysis or peritoneal dialysis or micro-dialysis or continuous venovenous hemofiltration or continuous venovenous hemodialysis.
12. Subject is anticipated to be treated with any of the following medications during the course of study therapy:
    a. Valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening)

[redacted]

b. Concomitant systemic (IV or oral) Gram-negative antibacterial agents in addition to those designated in the study treatment groups
c. Concomitant systemic (IV or oral) antifungal or antiviral therapy for the index infection of HABP/VABP.

13. Life expectancy is <3 days.
14. Subjects in refractory septic shock, defined as persistent hypotension despite adequate fluid resuscitation and vasopressive therapy at the time of randomization.
15. Subjects with 1 or more of the following laboratory abnormalities in baseline specimens: aspartate aminotransferase, alanine aminotransferase >3 × the upper limit of normal (ULN), total bilirubin level >2 × ULN (except for isolated hyperbilirubinemia due to known Gilbert's disease), neutrophils <500 cells/mm^3, platelet count <40,000/mm^3.
16. History of active liver disease or cirrhosis.
17. Subjects with an APACHE II score of >30.
18. A female who is pregnant or breastfeeding or has a positive pregnancy test as screening.
19. Subject is participating in any clinical study of any investigational medication (i.e., non-licensed medication) during the 30 days prior to randomization. COVID-19 vaccines that are given under emergency use authorization are not considered investigational agents.
20. Any other condition or prior therapy, which, in the opinion of the investigator, would make the subject unsuitable for this study.

4.3. Discontinuation Criteria

4.3.1. Screen Failures

Screen failures are defined as subjects from whom consent to participate in the clinical study is obtained, but who are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities.

4.3.2. Subject Discontinuation

The investigator has the right to discontinue a subject from study treatment or withdraw a subject from the study. In addition, subjects have the right to voluntarily discontinue study treatment or withdraw from the study at any time at his/her request for any reason.

In instances where a subject discontinues study treatment early, the investigator should strongly encourage the subject to continue the study and complete all scheduled visits, including any standard of care treatment. The site should continue to obtain vital status at Day 14 and Day 28 even if the subject withdraws consent. Rescue antibiotics are to be given to the subject as judged by the investigator. The discontinuation of study treatment will be registered in the IXRS.

Subjects who discontinue study treatment early and complete all scheduled visits will be considered study completers. If the subject is unwilling or unable to attend the scheduled site visits after hospital discharge, every effort should be made by the investigator (or qualified designee) to obtain data for the visits by either telephone, telemedicine, and/or home health visit.

Reasons for discontinuation of study treatment may include, but are not limited to:

- Insufficient therapeutic effect of the study drug (i.e., requirement for additional non-study antibacterial therapy to treat HABP/VABP based on the investigator's clinical judgment)
- AEs requiring discontinuation (e.g., hypersensitivity reactions based on investigator's clinical judgment)
- Any of the following post-baseline elevations in liver transaminase levels:
    - ALT or aspartate aminotransferase (AST) ≥8 × ULN
    - ALT or AST ≥3 × ULN, accompanied by total bilirubin >2 × ULN OR international normalized ratio >1.5
    - ALT or AST ≥3 × ULN, accompanied with signs and symptoms compatible with hepatitis.
- [redacted]
- Pregnancy
- Important protocol deviation (i.e., affecting the subject's safety) as judged by the investigator
- Investigator or sponsor determines it is in the best interest of the subject
- Subject withdrawal of consent to receive further study treatment.

Reasons for withdrawal from the study may include, but are not limited to:

- Subject, or his or her legally authorized representative, withdrawal of consent
- Subject lost to follow-up
- Death
- Study termination by the Sponsor, or investigator decision, or by regulatory authorities.

In instances where a subject withdraws consent prior to completion of study treatment, the investigator should strongly encourage the subject to complete the EOT assessments (see Table 9).

The primary reason for premature study drug treatment discontinuation and study withdrawal should be documented on the medical record and the appropriate electronic case report form (eCRF).

4.3.3. Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- Every effort should be made for subjects to complete the TOC visit as soon as possible. If the TOC visit is missed, but completed before the LFU window, the visit should be assessed as the TOC visit. Subjects should be counseled on the importance of maintaining the assigned visit schedule as outlined in the Schedule of Assessments (Table 9), and ascertain whether or not the subject wishes to and/or should continue in the study

- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4.4. Study Termination

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed, except for the sites without any subjects enrolled which could be administratively closed by a close-out letter.

Reasons for study termination may include, but are not limited to:

- AEs unknown to date (i.e., not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of drug development.

5. STUDY TREATMENTS

A detailed process for ordering, storage and preparation of final volume for the IV infusion for subjects with different renal functions, packaging and labeling of the IMP and comparator for administration are specified in the Pharmacy Manual.

5.1. Treatments Administered

All study drugs will be administered in a double-blinded manner. All study drugs (test and comparator) will be provided by the Sponsor to the site.

Intravenous linezolid or vancomycin will be allowed as local standard of care for the treatment of MRSA (see Section 6.1.2).

5.2. Investigational Medicinal Product (XNW4107 in Combination with Imipenem/Cilastatin)

5.2.1. Identity of XNW4107 for Injection

Below is a summary of the physical and chemical properties of the XNW4107.

Further details are presented in the IB (XNW4107 IB).

5.2.2. Imipenem/Cilastatin Pharmaceutical Form

Imipenem/cilastatin is a white to light yellow powder for solution for infusion in a glass vial.

The active substances are imipenem and cilastatin. Each vial contains imipenem monohydrate equivalent to 500 mg imipenem and cilastatin sodium equivalent to 500 mg cilastatin. The other ingredient is sodium bicarbonate.

XNW4107 will be supplied in a single dose 50R Type I glass vial sealed with a 20 mm rubber stopper and a 20-mm aluminum cap with flip-off seal. It is intended for administration by IV

infusion. Each vial containing nominal 250 mg of active ingredient XNW4107 is intended for reconstitution with normal saline (0.9% sodium chloride injection).

5.2.3. Preparation of Infusion

[redacted].

Imipenem/cilastatin will be reconstituted with saline according to the instructions of the Package Insert and the reconstituted suspension will be transferred to the IV infusion bag and mixed with XNW4107.

The mixed solution of XNW4107 and imipenem/cilastatin in one IV infusion bag will be further diluted with saline to a final volume of 100 mL. The dose and final infusion volume will be adjusted according to the renal function of the subject prior to the IV administration ([redacted].

The investigator or pharmacist at the investigational site will undertake specific training on handling and preparing study treatment and will ensure Good Pharmacy Practices are followed during the preparation and reconstitution process of IMI-XNW4107 infusion.

5.2.4. Administration of Infusion

[redacted].

5.3. Imipenem/Cilastatin/Relebactam

5.3.1. Pharmaceutical Form

IMI/REL is provided as single dose clear glass vials containing imipenem monohydrate equivalent to 500 mg imipenem, cilastatin sodium equivalent to 500 mg cilastatin, and relebactam monohydrate equivalent to 250 mg relebactam as a white to light yellow powder for injection.

5.3.2. Administration of Infusion

IMI/REL will be administered IV as 1.25 g dose (imipenem 500 mg/ cilastatin 500 mg/relebactam 250 mg) diluted in normal saline to a final volume of 100 mL and will be infused over 30 minutes (±5 minutes) q6h (±30 minutes) for subjects with eGFR ≥90 mL/min. Dose and final

infusion volume are adjusted according to renal function. See dose adjustments for lower renal function in Section 5.9. The detailed infusion volume adjustments are provided in the Pharmacy Manual. If the scheduled infusion starting time (±30 minutes) is missed, the subsequent infusion must return to the originally scheduled starting time of the IV infusion.

5.4. Packaging and Labeling

The final IMI-XNW4107 and IMI/REL infusions will be prepared by the investigational site pharmacy using standard institutional procedures and according to the Package Insert for imipenem/cilastatin and IMI/REL.

Adequate supplies of all study drugs will be provided to each investigational site.

The manufacture of drug product XNW4107 for injection will be carried out under GMP.

Labeling and packaging of IMI-XNW4107 and IMI/REL will meet applicable regulatory requirements and country-specific requirements and label text will be approved by the Sponsor. All drug shipment requests for IMI-XNW4107 and IMI/REL will be processed and approved by the Sponsor or designee. A complete record of batch numbers and expiry dates of all study drugs and labels will be maintained in the Sponsor's study file.

5.5. Storage and Stability

XNW4107 for injection (250 mg) must be stored in a secure area (e.g., a locked cabinet), protected from moisture, and kept at controlled temperature of 5°C (±3°C) until the time of preparation for study drug administration.

Imipenem/cilastatin should be stored as indicated in the Package Insert (see also the label).

For lower and normal dose groups, drug concentration of XNW4107 and imipenem and cilastatin is 2.5/5/5mg/mL or lower in final infusion solution, it is stable at room temperature of 25°C±2°C for 2 hours or at 5°C±3°C for 24 hours, respectively. For higher dose group, drug concentration of XNW4107 and imipenem and cilastatin is 3.75/7.5/7.5mg/mL in final infusion solution, it is stable at room temperature of 25°C±2°C for 2 hours or at 5°C±3°C for 8 hours, respectively. All stability and compatibility data show appropriate support for the planned clinical use. The color of the IV solution of XNW4107 and imipenem/cilastatin may turn from colorless (zero point) to slightly yellow or yellow (2°C to 8°C for 24 hours) which originates from the imipenem/cilastatin solution, however, this will not affect the potency which is described in the FDA-approved drug product label of imipenem/cilastatin.

IMI/REL should be stored as indicated in the Package Insert (see also label). A detailed process for handling and administration of IMI/REL will be specified in the Prescribing Information/Package Insert and SmPC.

5.6. Study Treatment Accountability, Reconciliation, and Return

Upon completion and termination of the study, all unused and/or partially unused study treatment shall be returned to the Sponsor or other authorized party if not authorized by the Sponsor to be destroyed at the site.

All study treatments returned to the Sponsor or other authorized party must be accompanied by the appropriate documentation and be clearly identified. Study treatment may only be returned after drug accountability is completed. Returned supplies should be in their original containers (component vials that have clinical labels attached).

Empty vials may not be destroyed until drug accountability is completed. Empty vials DO NOT need to be returned to the Sponsor. It is the investigator's responsibility to arrange disposal of all empty vials according to the institutional regulations.

The return or destruction of unused study treatment should be arranged by the site monitor.

5.7. Study Treatment Handling and Disposal

The Sponsor will be responsible for ensuring that the quality of the study treatment is adequate for the duration of the study.

It is the responsibility of the investigator or designee to ensure that the study treatment is only dispensed to the subject. The study treatment must be dispensed from official study sites by authorized personnel according to local regulations. The investigator or designee must maintain accurate records of the study treatment receipt, dispensing information, and disposition.

If study treatment is to be destroyed at the site, it is the investigator or designee's responsibility to ensure that arrangements have been made for disposal, drug accountability has been completed by the site monitor, procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures, and appropriate records of the disposal have been documented and provided to the Sponsor or designee.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.8. Method of Treatment Assignment

In this study, subjects will be randomized on Day 1 by IXRS, a computer-generated random sequence system. Randomization will be stratified by type of infection (non-ventilated HABP vs. ventilated HABP/VABP), APACHE II score (<15 vs. ≥15) (see Appendix 2), and country/region (China vs. Rest of World). The number of subjects randomized with ventilated HABP/VABP will be at least 50% of the randomized population.

Subjects will be randomized in a [redacted] ratio to receive either combination treatment IMI-XNW4107 administered IV q6h or IMI/REL administered IV q6h in a double-blinded fashion.

All study drugs will be dispensed from numerically coded containers. The code will remain with the IXRS until it is required for study unblinding following lock of the database.

5.9. Dose Modifications

No dose reduction is recommended in subjects with impaired hepatic function.

No dose adjustment is required for elderly subjects with normal renal function.

Dose adjustments will be required for subjects with abnormal renal function (see below) and will be based on the subject's calculated eGFR using the Modification of Diet in Renal Disease (MDRD) 4-variable equation.

MDRD equation (https://www.hepatitisc.uw.edu/page/clinical-calculators/mdrd)

> eGFR in mL/min per 1.73 m^2 = 175 × $SerumCr^{-1.154}$ × $age^{-0.203}$ × 1.212 (if subject is Black or African American) × 0.742 (if female).

Individual eGFR will be used to determine the requirement of dose adjustment. The individual eGFR (mL/min) is derived by (eGFR by MDRD/1.73 m^2) × BSA, where BSA is the individual body surface area calculated as: 0.20247 × height $(m)^{0.725}$ × mass $(kg)^{0.425}$. The eGFR will be referred to the individual eGFR in the unit of mL/min thereafter per the calculation described above if no unit of 1.73 m^2 is carried on.

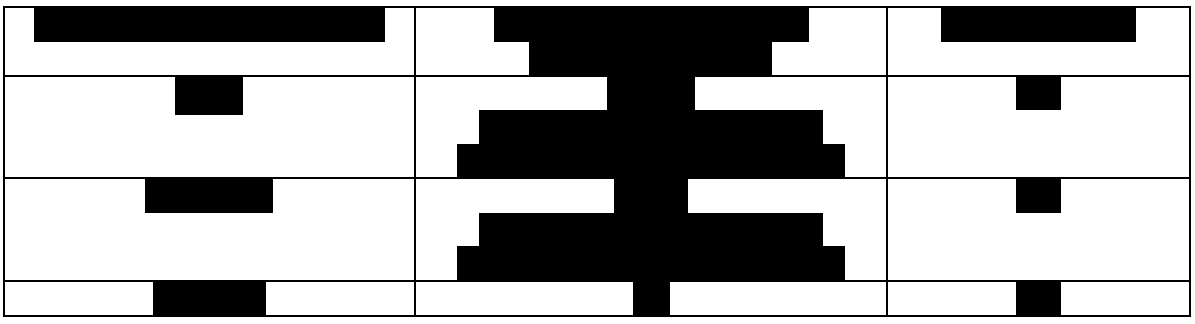
The eGFR will be calculated based on results from the local laboratory. The initial dose should be based on the calculated individual eGFR at screening. Since renal function can fluctuate quickly in ill subjects, renal function will be monitored daily during the first 3 days after initiation of study therapy, then subsequently, based on investigator's judgment, as clinically indicated. The local creatinine and individual eGFR calculated using MDRD will be recorded in the eCRF.

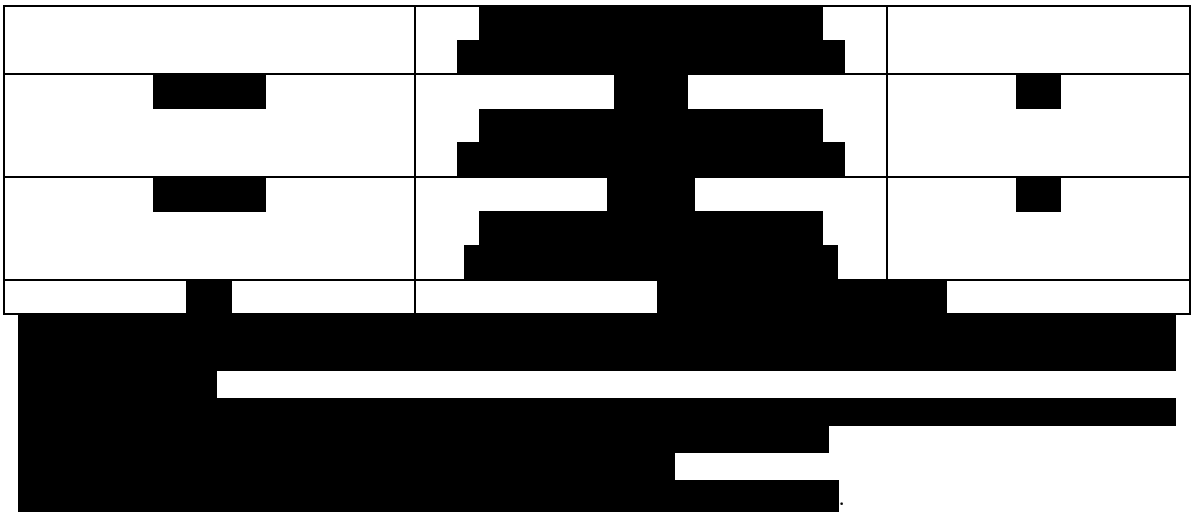
Refer to the Pharmacy Manual for specific instructions regarding preparation of doses following adjustments.

5.9.1. Imipenem/Cilastatin-XNW4107

Table 2 shows the recommended dose adjustments for IMI-XNW4107.

Table 2: Recommended Dosage of IMI-XNW4107, Given as 30(±5) -Minute Infusion, q6h (±30 minutes)





5.9.2. Imipenem/Cilastatin/Relebactam

IMI/REL dosage should be reduced in subjects with eGFR of <90 mL/min.

Table 3: Recommended IMI/REL Dosage Given as 30 (±5) - Minute Infusion, q6h (±30 minutes) to Adult Subjects with Normal Renal Function and Renal Impairment

Individual eGFR (mL/min)[a]	Recommended Dosage of IMI/REL (g)	Dosing Interval
≥90[b]	1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg)	q6h
60 to <90	1 g (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	q6h
30 to <60	0.75 g (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	q6h
15 to <30	0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	q6h
<15	Excluded from the study	

Abbreviations: BSA = body surface area; eGFR = estimated glomerular filtration rate; IMI/REL = imipenem/cilastatin/relebactam, MDRD = Modification of Diet in Renal Disease; q6h = every 6 hours.
a: calculated using the MDRD equation and individual BSA by (eGFR by MDRD/1.73 m^2) × BSA. Where BSA is the individual body surface area calculated as: 0.20247 × height $(m)^{0.725}$ × mass $(kg)^{0.425}$
Source: imipenem/cilastatin/relebactam label
b: subjects with individual eGFR ＞250 mL/min will also be excluded from the study.

5.10. Blinding

This is a double-blinded study.

All study personnel and subjects will be blinded to the treatment assignment with the exception of specific personnel as described in Table 4, and in a separate Maintaining Study Blind and Unblinding Plan.

Table 4: List of Unblinded Parties to Support the Study Conduct

Unblinded Parties	Reason to be Unblinded
Unblinded pharmacist(s) and/or other unblinded qualified personnel (e.g., unblinded nurse[s])	Reconstitute the study drug onsite, prepare the infusions for each day of dosing, and dispense either imipenem/cilastatin-XNW4107 or imipenem/cilastatin/relebactam in a blinded manner.
Unblinded CRA/Site Monitor	Review the unblinded pharmacist's documentation and oversee the drug dispensing activity periodically throughout the study. The unblinded CRA will have specific responsibility limited only to monitoring the work of the unblinded pharmacist at each study site.
Unblinded visit report and study file reviewers	Review of unblinded visit reports and periodic reviews of the unblinded sections of the Trial Master File
Drug supply chain and IRT vendor personnel	Responsible for production of the randomization scheme and have an unblinded inventory manager role in the IRT system for purposes of study drug inventory management.
Bioanalytical laboratory personnel	Facilitate PK sample management.
Independent biostatistician and programmers	Facilitate the DMC data reviews and safety surveillance.
Individuals in pharmacovigilance and regulatory	IND safety reporting and/or expedited reporting SUSARs to Health Authorities. These individuals are not part of the core study team and not directly involved in any study conduct.

Abbreviations: CRA = clinical research associate; DMC = Data Monitoring Committee; IND = investigational new drug; IRT = interactive response technology; PK = pharmacokinetics; SUSAR = suspected unexpected serious adverse reaction.

Covers will be provided for infusion bags and lines to maintain blinding.

To also preserve blinding, the active drug and IMI/REL will be identical in appearance.

Unblinding should only occur in the event of a medical emergency. Investigators should note that the occurrence of an SAE should not routinely precipitate the immediate unbinding of the label. When knowledge of the study drug is essential for the clinical management or welfare of the subject, the investigator may unblind a subject's treatment assignment. In the event of an emergency unblinding by the investigator, the Sponsor must be informed as soon as possible. The medical monitor is available to discuss the need to unblind any subject and can be contacted if needed.

For SUSAR (suspected, unexpected, serious adverse reactions) cases where the investigator has not broken the blind, the Sponsor will break the blind in accordance to Sponsor/clinical research

organization (CRO) global standard operating procedure before reporting to health authorities, institutional review boards (IRBs)/independent ethics committees (IECs) and investigators if the SUSAR was related to the blinded treatment. The information will be maintained in the Global Pharmacovigilance database.

Any reported SAEs that refer to a failure of the expected pharmacological action, are not considered SUSAR cases and are therefore exempted from unblinding.

5.11. Treatment Compliance

Since all treatments are administered at the clinical site by site personnel, the investigator or designee must maintain accurate records of all study treatments, including dates of study drug receipt, quantities received and dispensed, and batch/lot numbers. In addition, the study treatment must be noted in the subject's medical records and eCRF, with the date and time of administration and dose of each study treatment.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Prior and Concomitant Therapy

The investigator must record the use of all prior and concomitant medications (both prescribed and over-the-counter, including herbal remedies) or vaccines taken during 14 days prior to the first dose of study drug through the LFU visit in the source documents and eCRF along with:

- Reasons for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Subjects should receive full supportive care during and after the administration of IMI-XNW4107 injection or IMI/REL or standard of care treatment per local practice and according to the judgment of the investigator or treating physician.

Subjects should be discouraged from starting any new medication, both prescribed and over-the-counter, including herbal remedies without consulting the investigator unless the new medication is required for emergency.

6.1.1. Non-Antibiotic Concomitant Medications

Subjects are not permitted to take those medications specified in the exclusion criteria (Section 4.2), and the following below:

For subjects who will receive linezolid as Gram-positive adjunctive therapy, the following are prohibited:

- Prior use of a monoamine oxidase inhibitor within 14 days of the first dose of linezolid
- Concomitant use of any of the following medications during linezolid therapy:
    - Serotonin re-uptake inhibitors
    - Tricyclic antidepressants
    - Serotonin 5-HTI receptor agonists (triptans)
    - Meperidine
    - Buspirone
    - Monoamine oxidase inhibitors.

Investigator should also follow the local Prescribing Information for imipenem/cilastatin and IMI/REL when determining whether a medication should or should not be given.

In case of infusion-related reactions, administration of paracetamol and/or antihistamine drugs is acceptable.

All other concomitant medications necessary for the health and well-being of the subject which are permitted will be recorded (using the generic name) on the concomitant medications page of the eCRF.

COVID-19 vaccines that are given under emergency use authorization are not considered investigational agents.

6.1.2. Antibiotics Concomitant Medications

[redacted].

No sequential oral antibiotic (step-down) therapy is permitted.

Use of systemic antibacterial other than study drug therapy is not permitted during the study **except** in the following circumstances:

- Failure of study drug and need for rescue antibiotic therapy as judged by the investigator
- For the treatment of an AE (i.e., a new infection develops at a different site). The investigator should try to use an antibiotic not active against the baseline Gram-negative pathogen
- Use of antibiotics (not active against Gram-negative pathogens) for surgical prophylaxis
- Local care for superficial wounds is permitted (i.e., topical antiseptic therapy, topical antibiotic ointment, wet-to-dry dressing change). The use of topical antibiotic therapy with activity against Gram-negative organisms is discouraged, but will not constitute a failure of the primary antibiotic regimen if administered. Topical antifungal treatment or a single oral dose of any antifungal treatment of vaginal candidiasis will be allowed
- Oral vancomycin or other agents not active against Gram-negative pathogens for the treatment of *Clostridioides difficile* diarrhea will be allowed.

Optional linezolid as judged by the investigator can be given to subjects in both arms to provide coverage for MRSA as per local standard of care. 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.

6.1.3. Procedures and Surgeries

All concomitant diagnostic and therapeutic pulmonary procedures after the administration of the first dose of study drug through the LFU visit should be recorded in the eCRF. Concomitant diagnostic or therapeutic procedures clinically relevant to the pneumonia under study or any SAE should be reported in the eCRF. **Note:** Repeat pulmonary imaging studies that are not significantly changed do not need to be reported.

6.2. Contraception

Where sexually active, female subjects of childbearing potential (defined as women who are not surgically or chemically sterilized and who are between menarche and 1 year post-menopause / 2 years of amenorrhea) must be willing to use highly effective methods of contraception from the signing the informed consent form (ICF) through 1 month after receiving the last dose of study treatment to minimize the pregnancy risk.

Highly effective contraception methods are defined as those that result in a low failure rate (<1% per year) when used consistently and correctly. Such methods include a sterile sexual partner, hormonal contraceptives (oral, injection, transdermal patch, or implant), or intrauterine device to prevent pregnancy for at least 3 months prior to study drug administration. Also, refer to inclusion #10 for details (Section 4.1).

Male subjects with female sexual partners of childbearing potential must be willing to use medically acceptable birth control for 90 days following the last dose of study medication. Sexual abstinence, vasectomy, or a condom used with a spermicide are medically acceptable birth control methods for males. Male subjects must agree not to donate sperm for a period of 90 days after the last dose of study treatment.

7. STUDY ASSESSMENTS AND PROCEDURES

A summary of procedures or assessments to be performed at each visit is provided in Section 7.1 through Section 7.3. Details for each of the procedures are provided in Section 7.5 (efficacy), Section 7.6 (safety and tolerability), and Section 7.7 (PK).

7.1. Screening Procedures

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria within 24 hours (except chest imaging) prior to randomization. Chest imaging must be completed and eligibility confirmed within 48 hours prior to randomization. Appropriate clinical specimen (lower respiratory specimen and blood for culture) must be obtained from all subjects within 48 hours prior to randomization.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (Section 4.3.1), as applicable. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, chest imaging) and obtained within 24 hours prior to randomization (or 48 hours for chest imaging) may be utilized for screening eligibility.

All screening laboratory, baseline (screening or Day 1 before the first dose of study drug) and post-baseline safety laboratory tests will be performed locally.

The maximum amount of blood from each subject over the duration of the study including any extra assessments that may be required will not exceed volumes as stated by local regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Subjects cannot be rescreened. However, assessment (e.g., eGFR) can be repeated within the 24-hour screening window period if the initial assessment failed to meet eligibility.

The following procedures or assessments will be performed:

- Informed consent
- Inclusion/exclusion criteria (eligibility review)
- Demographics: sex, race, age and ethnicity. Race will be collected only in countries that permit
- Medical history
- Prior and concomitant medications or vaccines taken within 14 days prior to the planned first dose of the study drug
- Standard physical examination

[redacted]

[redacted]

7.2. Treatment Period (Day 1 to Day 14)

Subjects may receive treatment for a recommended duration of 7 to 14 calendar days (judged by the investigator).

7.2.1. Randomization (Day 1)

Stratification in IXRS will be done at the time of randomization. If screening and randomization [redacted]

The following procedures or assessments will be performed before the first dose administration:

- Prior and concomitant medications
- Concomitant diagnostic and therapeutic procedures
- Symptom-oriented physical examination

[redacted]

5.9

[redacted]

7.5.4

[redacted]

- Survival
- Record AEs.

7.2.2. Day 2 to Day 3

The following procedures or assessments will be performed:

- Concomitant medications
- Concomitant diagnostic and therapeutic procedures

- Symptom-oriented physical examination

[redacted]

- Record AEs.

7.2.3. Day 4

The following procedures or assessments will be performed:

- Concomitant medications
- Concomitant diagnostic and therapeutic procedures
- Symptom-oriented physical examination

[redacted]

[redacted]

- Survival
- Record AEs.

7.2.4. Day 5 to Day 14

The following procedures or assessments will be performed:

- Concomitant medications
- Concomitant diagnostic and therapeutic procedures
- Symptom-oriented physical examination

[redacted]

[redacted]

- Record AEs.

7.3. End of Treatment, Test-of-Cure, and Late Follow-Up Assessments

The EOT visit will occur on the day of last IV study therapy or the day after. Duplication of assessments for a given day and EOT is not necessary. If EOT occurs on Day 14, survival needs to be evaluated.

[redacted]

The following procedures or assessments will be performed:

- Concomitant medications
- Concomitant diagnostic and therapeutic procedures

- Symptom-oriented physical examination

[redacted]

- [redacted]
- Record AEs.

7.4. Unscheduled Assessments

Unscheduled assessments may be conducted at any time according to the investigator's discretion, as clinically appropriate.

7.5. Efficacy Assessments

7.5.1. Assessment of HABP/VABP Signs and Symptoms

Infection-specific clinical signs and symptoms will be evaluated by the investigator at each specified visit in the Schedule of Assessments (Table 9) to determine the clinical response assessment.

Signs and symptoms specific to HABP/VABP including expectorated sputum production, increased tracheal secretions, cough, dyspnea, pleuritic chest pain, wheezing, rales, tachypnea, rhonchi, egophony, dullness to percussion, and bronchial breath sounds will be assessed at baseline as absent, mild, moderate, severe, or unknown.

Whenever possible the same person should conduct these assessments for any given subject throughout the study.

7.5.1.1. Oxygenation Status

The subject's oxygenation status, including PaO_2, FiO_2, and O_2 saturation, will be assessed at the specified visits in the Schedule of Assessments (Table 9). The oxygenation status will be determined by arterial blood gases or pulse oximetry. [redacted]

[redacted].

7.5.1.2. Status of Ventilator Support

[redacted]

7.5.2. Chest Imaging

Chest imaging (Chest x-ray or computed tomography scan) will be performed at screening and is required for diagnosis and assessment of eligibility. [redacted] The investigator's (or qualified designee's at the site) interpretation of the chest imaging may be used to make the enrollment decision if a radiologist's interpretation is not available.

Local reading of screening chest imaging by a radiologist is required for all subjects including subjects enrolled based on the interpretation of the investigator. The local radiologist's interpretation will be captured.

Details on the interpretation from both the investigator (if used for enrollment) and the radiologist report will be collected including the presence and location of pneumonia findings such as infiltrates, opacities, and consolidation for all screening films. In addition, any radiology reports will be collected if relevant to an SAE as well as follow-up reports if results are clinically significant.

7.5.3. APACHE II Score

APACHE II score will be collected and used as a method to establish the severity of disease at screening. The APACHE II score calculation will be based on details provided in Appendix 2, and entered in the eCRF at screening by the investigator or qualified designee.

7.5.4. SOFA Score

The SOFA is a scoring system to determine the extent of a subject's organ function or rate of failure. The investigator or qualified designee will record the components required to calculate a SOFA score (see Appendix 3). Daily SOFA will be done while the subject is in the ICU based on local laboratory tests from samples obtained as standard of care. The most recent available laboratory results will be used to calculate the SOFA score. No additional laboratories samples will be obtained beyond the local standard of care. The local laboratory tests must include the required parameters for SOFA scoring: platelets, total bilirubin, creatinine if not using urine output, and oxygen saturation if PaO_2 is not available (Oxygen saturation can be converted to PaO_2 for the SOFA score calculation). Refer to Table 9 for timings of SOFA assessment.

7.5.5. GCS Score

The GCS is an adopted standard for assessment of impaired consciousness and coma in acutely ill trauma and non-trauma subject and assists with predictions of neurological outcomes (complications, impaired recovery) and mortality. The investigator or qualified designee will record the components required to calculate GCS (see Appendix 4), and use it to complete the APACHE II and SOFA scores. Daily GCS will be done while the subject is in the ICU. Refer to Table 9 for timings of GCS assessment.

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted].

7.5.10. Survival

[redacted]

[redacted]

7.6. Safety and Tolerability Assessments

Safety endpoints will be assessed by review of AE summaries which will include SAEs, unless stated otherwise. Adverse events will be categorized by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and the severity of AEs will be assessed.

7.6.1. Adverse Events

Adverse events will be monitored throughout the study. Serious AEs will be collected from the time informed consent is signed and non-serious AEs from the first dose of study treatment until LFU visit.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

7.6.1.1. Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. This includes the following:

- Any clinically significant worsening of a pre-existing condition

Note: Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered an AE

- Any recurrence of a pre-existing condition

- An AE occurring from an overdose of a Sponsor study drug whether accidental or intentional (i.e., a dose higher than that prescribed by a health care professional for clinical reasons)

- An AE occurring from abuse of a Sponsor study drug (i.e., use for non-clinical reasons)

- An AE that has been associated with the discontinuation of the use of a Sponsor study drug.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the informed consent and that is documented as part of the subject's medical history. Pre-existing medical conditions/diseases/symptoms that worsen after signing the informed consent are SAEs/AEs. However, only SAEs will be collected from the time informed consent is signed while non-serious AEs will be collected from the first dose of study treatment.

An AE or SAE will be considered treatment-emergent if they occur any time after the first dose of study treatment.

In case of fatality, the cause of death is considered as the SAE, and the death is considered as its outcome, and the end date of the SAE is the date of death.

Information about all AEs, whether volunteered by the subject, discovered by the investigator or designee questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded, as appropriate.

All AEs will be treated appropriately. Such treatment may include discontinuation of study treatment, if necessary.

Events associated to progression of the disease under study (e.g., progression of pneumonia) are not reported as AEs.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity or intensity of the AE using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 grading as shown below:

- **Grade 1:** Mild; usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living

- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated, disabling

- **Grade 4:** Life-threatening consequences; urgent intervention indicated

- **Grade 5:** Death related to AE.

The CTCAE can be found via the website: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

Relationship to Study Treatment

The investigator will make a determination of the relationship of the AE to the study drug using a five-category system according to the following guidelines:

- **Not Related:** when the AE is definitely caused by the subject's clinical state, or the study procedure/conditions
- **Unlikely Related:** when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE
- **Possibly Related:** when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- **Probably Related:** when the AE follows a reasonable temporal sequence from the time of drug administration but could not have been produced by the subject's clinical state or the study procedures/conditions
- **Definitely Related:** when the AE follows a reasonable temporal sequence from the administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

For the purposes of Investigational New Drug safety reporting, the below will be considered:

Causality Assessment Options (from SAE form / EDC)	Considered Related?
Not related	Considered not related
Unlikely related	
Possibly related	Considered related
Probably related	
Definitely related	

Action Taken with Study Treatment for Adverse Events

The investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose Not Changed:** The medication schedule was not changed

- **Drug Interrupted:** The medication schedule was modified by temporarily terminating the prescribed regimen of medication
- **Drug Withdrawn:** The medication schedule was modified through termination of the prescribed regimen of medication
- **Not Applicable**
- **Unknown**

Serious Adverse Events

An SAE is any AE occurring at any dose that meets one or more of the following criteria:

- Results in death
- Is life-threatening (see below)
- Requires subject hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Results in an important medical event (see below).

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening AE*** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization or prolongation of hospitalization is considered an SAE criterion. In the absence of an AE, the participating investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.

- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.

- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study). Hospitalization is to be considered only as an overnight admission.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the subject's bodily function/structure, physical activities, or quality of life).

If there is any doubt as to whether a case constitutes an AE or SAE based on the information available, the case should be treated as an SAE.

Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity. These include events that may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious.

Toxicities that fall within the SAE definitions listed above must be reported as an SAE regardless of whether they are felt to be treatment-related or not. Toxicities unrelated to treatment that do NOT fall within the SAE definitions above must be documented as AEs in the subject's source documents and eCRF.

Suspected Unexpected Serious Adverse Reactions

SUSARs are serious events with at least a reasonable possibility to be causally related to the IMP and/or comparator drug, that are not listed in the applicable product information (e.g., IB for an unapproved Investigational medicinal product). Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.

For XNW4107, the reference document for definition of expectedness is the Reference Safety Information from globally approved version of IB at the time of start date of the event.

For imipenem/cilastatin the reference document for assessment of expectedness is the current United States Prescribing Information (USPI) or/and SmPC for this product.

For comparator (Imipenem/Cilastatin/Relebactam), the reference document for assessment of expectedness is the current United States Prescribing Information (USPI) or/and SmPC for this product.

7.6.1.2. Reporting Adverse Events

Reporting of Adverse Events

At each visit, the investigator or delegate will determine whether or not any AEs have occurred. Non-leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the subject to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the eCRF and in the subject's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

Reporting of Serious Adverse Events

All SAEs, occurring after the signing of the ICF until LFU visit and regardless of study drug relationship, must be entered into the clinical database and the investigator or delegate must report the SAE(s)/pregnancy reports to the Sponsor or designee within 24 hours of obtaining knowledge of the event, by reporting the SAE electronically via the eCRF and pregnancy reports via paper form, or in case of eCRF unavailability, by emailing a copy of a paper SAE form to SAEIntake@labcorp.com and safety@evopointbio.com for cases occurred in ex-China. For cases occurred in China, the China investigator will directly complete a China-specific manual SAE/pregnancy report, including date and signature and send to safety@evopointbio.com within 24 hours of awareness.

The initial SAE form must contain as much information as possible and be updated if more information becomes available.

[redacted]

The trial site should notify the site monitor via phone or email about the submission of the SAE report.

All sites will follow their institutional requirements for submission of SAEs to their IRBs/IECs.

The Sponsor should be notified if the investigator becomes aware of any SAEs/Pregnancies that occur after the end of the SAE reporting period and is believed to be related to prior study treatment. The investigator should report these post-study events to the Sponsor via email 4107Safety@evopointbio-us.com and safety@evopointbio.com.

7.6.1.3. Follow-up of Adverse Events/Serious Adverse Events

Adverse events/SAEs will be followed until resolution or stabilization of the event, completion of the subject's participation, or study termination, or the investigator or designee and Sponsor agree that follow-up is no longer necessary, whichever occurs first.

Assessments should be made at each visit (or more frequently, if necessary) of any changes in severity, the relationship to the study drug, the intervention required to treat it, and the outcome.

Side effects known for XNW4107 or imipenem/cilastatin or IMI/REL are provided in the XNW4107 IB or respective Prescribing Information or SmPCs. All AEs will be immediately recorded in the subject's source documents.

7.6.1.4. Procedures for Recording Adverse Events

7.6.1.4.1. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between clinical visits. Such events should only be recorded once on the AE eCRF page. The initial severity of the event will be recorded at the time the event is first reported. If the severity or seriousness of a persistent AE changes a new record should be added on the AE eCRF page to report each severity or seriousness change with the corresponding start/end date. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 7.6.1.2 for reporting instructions).

A recurrent AE is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the AE eCRF page.

7.6.1.4.2. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if clinically significant by meeting any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin ≥5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the AE eCRF page.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF page, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the AE eCRF page (see Section 7.6.1.4.1) for details on recording persistent AEs).

7.6.1.4.3. Vital Sign Abnormalities

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if clinically significant by meeting any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy.

It is the investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE and further investigated as clinically indicated.

7.6.1.4.4. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History eCRF page.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens from the first start dose to the LFU visit. When recording such events on the AE eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

7.6.1.4.5. Adverse Events Associated with an Overdose or Error in Treatment Administration

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF page.

All AEs associated with an overdose or incorrect administration of study drug should be recorded

on the AE eCRF page. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.6.1.2 for reporting instructions).

7.6.1.4.6. Planned Hospitalizations

A hospitalization planned prior to the first dose of study medication is considered a therapeutic intervention and not the result of a new AE. If the planned hospitalization or procedure is executed as planned, it should be recorded in the subject's medical history. However, if complications arise during the planned hospitalization or procedure or the subject experiences an AE during the planned hospitalization or procedure, it must be reported as an AE.

7.6.1.5. Investigator's Notification of Adverse Events to the Sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigational site file. This information will be updated as needed. Serious AEs occurring during the study must immediately (within 24 hours of investigator awareness) be reported per Section 7.6.1.2.

Serious AEs occurring after the protocol-defined observation period will be processed by the Sponsor according to applicable regulations.

7.6.1.6. Expedited Reporting of Adverse Events to Regulatory Agencies/Authorities

7.6.1.6.1. Notification to the Independent Ethics Committee/Institutional Review Board

Notification to the IEC/IRB about all relevant events (e.g., SAEs/SUSARs) will be performed by the Sponsor or Sponsor's designee and/or by the investigator according to all applicable rules/regulations.

7.6.1.6.2. Notification to the Authorities

The processing and reporting of all relevant events (e.g., SAEs) to the authorities will be done by the Sponsor or Sponsor's designee and/or by the investigator according to all applicable rules/regulations.

7.6.1.6.3. Sponsor's Notification to the Investigational Site

The Sponsor or designee will inform all investigational sites about reported relevant events according to applicable regulations. The Sponsor or Sponsor's designee will send the events to a site once the site initiation visit has occurred and will stop sending to the site once the last subject has completed their LFU visit.

7.6.1.7. Post-Study Adverse Events

The Sponsor should be notified if the investigator becomes aware of any SAEs that occur after the end of the AE reporting period and is believed to be related to prior study treatment.

The investigator should report these post-study events to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

7.6.1.8. Pregnancy

Although not considered an AE, it is the responsibility of the investigator or their designee to report any pregnancy in a subject or the subject's sexual partner that occurs during the study. All subjects who become pregnant must immediately discontinue the study drug and be withdrawn from the study. The subject or subject's sexual partner will be followed to completion/termination of the pregnancy. This information is important for both drug safety and public health concerns. If a subject is found to be pregnant after the study treatment was administered, the investigator should report this to the CRO and Sponsor within 24 hours and document the pregnancy either by electronic media or paper.

The investigator must make every effort to follow the subject until completion/termination of pregnancy. If the events during the pregnancy and/or outcome of pregnancy (i.e., complications regarding mother/baby) meet the criteria for classification of an SAE, the investigator must follow the procedures for reporting SAEs.

7.6.2. Clinical Laboratory Evaluations

All Screening laboratory tests will be performed locally to assess study eligibility. The list of required local laboratory tests is in Appendix 1. Baseline and post-baseline safety laboratory tests will also be performed locally. The timepoints at which these samples will be collected are shown in the Schedule of Assessments (Table 9)

The total volume to be drawn in the study may vary based on local/regional specific laboratory requirements.

A full list of laboratory parameters is provided in Appendix 1.

The investigator will record on the laboratory report his/her medical opinion of the clinical significance of all laboratory values that are outside the laboratory reference range. The investigator will sign and date each laboratory report form. Clinically significant laboratory findings made after the start of study medication that meet the definition of an AE must be recorded on the eCRF (see Section 7.6.1.1 and Section 7.6.1.4.2).

The investigator will provide the Sponsor or Sponsor's designee with a copy of each laboratory's certification and a tabulation of the normal ranges.

7.6.2.1. Pregnancy Testing

Urine or serum pregnancy test only for females who are not postmenopausal or surgically sterile. A serum pregnancy test will be performed at screening on females of childbearing potential. If the results of the serum β-human chorionic gonadotropin (β-hCG) cannot be obtained prior to dosing of IMP, a subject may be enrolled on the basis of a negative urine pregnancy test, though serum β-hCG must still be obtained.

7.6.2.2. Stool Samples

If a subject experiences significant diarrhea during or after study therapy, the investigator is strongly recommended to obtain a stool sample and test locally for *Clostridioides difficile*.

7.6.3. Vital Signs, Physical Examination, and Other Safety Evaluations

7.6.3.1. Vital Signs

Measurement of vital signs will include an assessment of HR, systolic and diastolic BP, body temperature, and RR.

Vital signs should be collected daily while on IV study therapy and at other timepoints/visits as specified in the Schedule of Assessments (Table 9). Collection on Day 1 should be performed prior to initiation of IV therapy.

Subject should be resting in a seated or semi-recumbent position for at least 5 minutes prior to having vital sign measurements obtained. For subjects who cannot sit up, HR, BP, and RR may be taken in a supine or semi-recumbent position.

Body temperature may be taken per the site's preferred method (i.e., one of core temperature [tympanic, rectal, or esophageal], oral and axillary temperatures). Method of measuring body temperature will be recorded in the appropriate eCRF. The same method of measuring a subject's body temperature should be used throughout the study.

Refer to Section 7.6.1.4.3 for vital sign abnormalities.

7.6.3.2. Physical Examination

Standard physical examination will be performed at screening. Unscheduled physical examination (standard or symptom directed) may be performed as needed.

Standard physical examinations include body weight and height, general appearance, skin/subcutaneous tissue, head, ears, nose, throat, neck and thyroid, thorax, lungs, cardiovascular, lymph nodes, abdomen, musculoskeletal, and neurological examinations. Genitalia, rectal, and breast examinations will only be performed if medically indicated.

Symptom-oriented physical examinations will be performed daily during IV study therapy after screening. This is a target physical examination based on the investigator's judgment of the subject's symptoms.

Abnormal findings on physical examination will be documented in the source documentation and eCRF. New or worsened clinically significant abnormalities should be recorded as AEs, if applicable.

7.6.3.3. 12-Lead Electrocardiogram

All subjects will have a standard 12-lead ECG performed locally at screening and at EOT visit. Additional ECGs can be performed as clinically indicated. The ECG will be performed after the subject has been in a supine or semi-recumbent position for at least 5 minutes.

The following ECG parameters will be recorded: HR, PR interval, R-R interval, QRS duration, QT interval, and diagnostic statements. The QTc data will be calculated using Fridericia's correction.

The investigator will assess whether the ECG is normal or abnormal, if abnormal, was it clinically significant or not. The results of this ECG evaluation and its interpretation will be captured. Any clinically significant abnormalities should be reported as AEs or medical history on the eCRF.

7.7. Pharmacokinetic Analysis

[redacted]

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

Assuming an all-cause mortality rate of 10% at Day 14 for both treatment groups, a [redacted] randomization ratio, and a one-sided significance level of 0.025, a study of approximately 450 subjects will have more than 90% power to show non-inferiority with a 10% non-inferiority margin.

A blinded sample size re-estimation will occur after approximately [redacted] subjects (approximately [redacted] and have 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. The sample size may be increased if required.

8.2. Analysis Populations

There are 9 analysis populations for this study:

Intent-to-Treat (ITT) population: All subjects who are randomized. Subjects are analyzed according to the randomized treatment, regardless of the treatment actually received.

SAF population: 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.

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.

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.

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

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.

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.

ME population: All subjects from the micro-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 microbiological outcome, and have no missing nor indeterminate assessment of microbiological outcome.

[redacted]

8.3. General Considerations for Data Analyses

Complete details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan. Statistical analysis will be performed using SAS System, version 9.4 or higher (SAS Institute, Inc., Cary, NC).

In general, continuous data will be presented using descriptive statistics: number of subjects, mean, standard deviation, minimum, the first quartile, median, the third quartile, and maximum. Geometric means and coefficient of variation will also be provided where applicable. Categorical data will be presented as frequencies with percentages per category. All reported confidence intervals (CIs) will be two-sided 95% CIs.

Summary data will be presented by treatment group and overall, and when applicable, by assessment time. Individual subject data will be listed by subject number, and, where applicable, by assessment time.

8.4. Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be presented using descriptive statistics for continuous and categorical data.

8.5. Medical History and Prior/Concomitant Medications

Medical history records will be summarized using descriptive statistics by SOC and PT within each SOC.

Prior/concomitant medications will be summarized separately using descriptive statistics for categorical data.

8.6. Efficacy Analysis

8.6.1. Estimand for the Primary Endpoint

[redacted]

[redacted]

8.6.1.2. Primary Efficacy Analysis

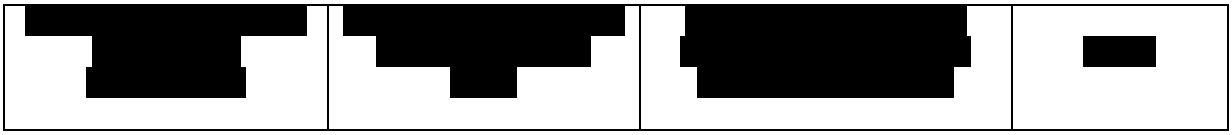
[redacted]

8.6.1.1

[redacted]

Koch, 1989

[redacted]



[redacted]

8.6.2. Secondary Efficacy Analysis

[redacted]

8.6.3. Exploratory Efficacy 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.

8.7. Safety and Tolerability Analysis

Safety and tolerability will be evaluated by presenting summaries of treatment-emergent AEs, routine clinical laboratory evaluations, vital signs, physical examination findings, and ECGs for each treatment group and overall.

All safety and tolerability analyses will be performed using the SAF.

All analyses of safety and tolerability endpoints will be descriptive only, and no inferential statistics will be provided.

8.7.1. Adverse Events

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

Summary tables will be provided for all TEAEs by treatment group. The number and percentage of subjects with TEAEs, related TEAEs, SAEs, and TEAEs leading to discontinuation of the study treatment will be presented by the current MedDRA version, SOC and PT. In addition, the number and percentage of subjects with TEAEs will be presented by SOC and PT by maximum severity.

In the TEAE summaries, subjects will be counted only once for each SOC if one or more TEAEs are reported. Similarly, subjects with more than one episode of a TEAE will be counted only once within a PT.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT.

Listings will be produced for all AEs (TEAEs and non-treatment-emergent). In addition, listings will be provided for those subjects who experience an SAE, including death, or who experience an AE associated with early withdrawal from the study or from study drug.

8.7.2. Clinical Laboratory Evaluations

Clinical laboratory data (including abnormal laboratory values and changes in abnormalities) will be summarized using descriptive statistics for continuous or categorical variables by visit. Where appropriate, absolute change from baseline will also be presented.

Selected clinical laboratory data will be presented graphically using scatterplots and/or boxplots.

Clinical laboratory tests data will be listed.

8.7.3. Vital Signs

Descriptive statistics of vital signs measurements and their change from baseline at each visit will be presented by treatment group.

8.7.4. Physical Examination

Physical examination findings will only be listed for each subject.

8.7.5. 12-Lead Electrocardiogram

Descriptive statistics will be provided. The ECG results (including QTc change) will be summarized by treatment group and will also be listed.

8.8. Pharmacokinetic Analysis

Concentration-time data for XNW4107, imipenem, and cilastatin will be analyzed and summarized by analyte using descriptive statistics (number of subjects, arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) at each scheduled collection time interval. Concentration-time data will be displayed graphically on the linear and semi-logarithmic scales.

[redacted].

8.9. Data Monitoring Committee

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.

8.10. Data Review Committee

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted] DRC Charter

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10. APPENDIX

Appendix 1 – Clinical Laboratory Evaluations

All screening laboratory tests will be performed locally to assess study eligibility.

The screening laboratory parameters required for determination of subject eligibility are listed in Table 5, of note, there are some parameters as follows must be done（ indispensable ） to ensure these are included in local clinical laboratory evaluations.

Hematology must include:

- CBC with WBC differential
- Platelets
- Hematocrit
- Optional #1: Greater than 15% immature neutrophils (bands) noted on peripheral blood smear (not mandatory)

Serum Chemistry must include:

- ALT, AST and Total Bilirubin
- Creatinine
- Sodium
- Potassium
- Serum bicarbonate if ABG is not performed

Serum pregnancy test

Urine pregnancy test is required if not feasible to obtain results of serum pregnancy test prior to randomization.

The following clinical laboratory analytes will be assessed at screening, baseline and post-baseline locally:

Table 5: list of clinical laboratory analytes

Chemistry	**Hematology (CBC):**
Albumin	Hematocrit
ALP	Hemoglobin
ALT	MCH
AST	MCHC
BUN/Urea	MCV
Calcium	Platelet count
Chloride	RBC count
Cholesterol	WBC count
Creatinine	WBC differential
GGT	(% & ABS):
Glucose	Basophils
LDH	Eosinophils
Phosphorus	Lymphocytes
Potassium	Monocytes
Sodium	Neutrophils
Total bilirubin	
Total CO_2 (measured as bicarbonate)*	**For women with childbearing potential only (only at screening):**
Total protein	Serum pregnancy test
Triglycerides	Urine pregnancy test
Uric acid	
Urinalysis (UA):	**Renal Function**
Color and/or appearance	eGFR
pH and specific gravity	
Bilirubin	**Coagulation**
Glucose	Prothrombin time
Ketones	Partial thromboplastin time
Leukocytes	INR
Nitrite	
Occult blood	
Protein	
Microscopic (including RBCs and WBCs)	

Abbreviations: ABS = absolute; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

*： Total CO2 is mandatory only when bicarbonate or pH of ABG is not performed.

Appendix 2 - APACHE II Score

The Acute Physiology and Chronic Health Evaluation II is a severity of disease classification system (Knaus, 1985), one of several intensive care unit (ICU) scoring systems. After admission of a subject to an ICU, an integer score from 0 to 71 is computed based on several measurements; higher scores imply a more severe disease and a higher risk of death.

APACHE II was designed to measure the severity of disease for adult subjects admitted to ICUs. The lower age is not specified in the original article, but a good limit is to use APACHE II only for subjects age 15 or older.

This scoring system is used in many ways:

- Some procedures and some medicine is only given to subjects with certain APACHE II score
- APACHE II score can be used to describe the morbidity of a subject when comparing the outcome with other subjects
- Predicted mortalities are averaged for groups of subjects in order to specify the group's morbidity.

Even though newer scoring systems, like Simplified Acute Physiology Score II (SAPS II) have replaced APACHE II in many institutions, APACHE II continues to be used extensively because so much documentation is based on it.

The point score is calculated from 12 routine physiological measurements (such as blood pressure, body temperature, heart rate, etc.) The calculation method is optimized for paper schemas. The resulting point score should always be interpreted in relation to the illness of the subject.

After the initial APACHE II score has been determined, no new score can be entered for this study during the hospital stay.

The appendix of the document that originally described the APACHE II score describes how to calculate a predicted death rate for a subject. In order to make this calculation of predicted mortality precise, the principal diagnosis leading to ICU admission was added as a category weight: the predicted mortality is computed based on the subject's APACHE II score and their principal diagnosis at admission.

For convenience to the sites, a website that can be used to calculate APACHE II score is provided below as an example of tools for APACHE II calculation:

https://www.mdcalc.com/calc/1868/apache-ii-score

Table 6: The APACHE II Severity of Disease Classification System

Physiologic Variable	**High Abnormal Range**				**Low Abnormal Range**				
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
Temperature – Rectal*(°C)	≥41	39 to 40.9		38.5 to 38.9	36 to 38.4	34 to 35.9	32 to 33.9	30 to 31.9	≤29.9
Mean Arterial Pressure -mmHg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5
Oxygenation: A-aDO_2 **or** PaO_2 (mmHg) a. FIO_2 ≥0.5 record A-aDO_2 b. FIO_2 <0.5 record PaO_2	≥500	350 to 499	200 to 349		<200 >70	61 to 70		55 to 60	<55
Arterial pH (preferred) **or** Serum HCO_3 (venous mEq/L) (not preferred, but mayuse if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15
Serum Sodium (mEq/L)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110
Serum Potassium (mEq/L)	≥7	6 to 6.9		5.5 to5.9	3.5 to5.4	3 to 3.4	2.5 to2.9		<2.5
Serum Creatinine (mg/dL) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6		
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20

White Blood Cell Count (total/mm^3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1
Glasgow Coma Score(GCS)	Score = 15 minus actual GCS								
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) ≤44 = 0; 45 to 54 = 2; 55 to 64 = 3; 65 to 74 = 5; ≥75 = 6 C. Chronic Health Points (see below)									
Total APACHE II Score (add together the points from A+B+C)									

Abbreviations: A-aDO_2 = alveolar-arterial pressure difference for oxygen; ABG = arterial blood gas; APACHE II = Acute Physiology and Chronic Health Evaluation II; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Comma Score; PaO_2 = partial pressure of oxygen.

* If core temperature measurement is not available (i.e., tympanic, rectal, esophageal), oral and axillary temperatures could be adjusted by adding 0.5°C and 1°C, respectively.

Chronic Health Points: If the subject has a history of severe organ system insufficiencyor is immunocompromised as defined below, assign points as follows: 5 points for non-operative or emergency postoperative subjects and 2 points for elective postoperative subjects.

Definitions: organ insufficiency or immunocompromised state must have been evidentprior to this hospital admission and conform to the following criteria:

- **Liver** – biopsy-proven cirrhosis and documented portal hypertension; episodes ofpast upper gastrointestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma
- **Cardiovascular** – New York Heart Association Class IV
- **Respiratory** – chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (e.g., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension [>40 mmHg], or respirator dependency)
- **Renal** – receiving chronic dialysis
- **Immunocompromised** – the subject has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection [e.g., leukemia, lymphoma, AIDS]).

Appendix 3 – Sequential Organ Failure Assessment Score

The sequential organ failure assessment (SOFA) score is a simple and objective score that allows for calculation of both the number and the severity of organ dysfunction in 6 organ systems (respiratory, coagulation, hepatic, cardiovascular, neurological, and renal), and the score can measure individual or aggregate organ dysfunction.

For convenience to the sites, a website that can be used to calculate SOFA score is provided below as an example of tools for SOFA scoring:

https://www.mdcalc.com/calc/691/sequential-organ-failure-assessment-sofa-score

Table 7: Sequential Organ Failure Assessment Score

The Sequential Organ Failure Assessment (SOFA) Score[a]					
	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mmHg	> 400	≤ 400	≤ 300	≤ 200[b]	≤ 100[b]
Coagulation Platelets $\times 10^3/\mu L$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, mg/dL[c]	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure < 70 mmHg	Dop ≤ 5 or dob (any dose)[d]	Dop > 5, epi ≤ 0.1, ornorepi ≤ 0.1[d]	Dop > 15, epi > 0.1, or norepi > 0.1[d]
Central Nervous System Glasgow Coma Score Scale	15	13 - 14	10 - 12	6 -9	< 6
Renal Creatinine, mg/dL or Urine Output, mL/d[e]	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 or < 500	≥ 5.0 or < 200

Abbreviations: dob = dobutamine, Dop = dopamine, epi = epinephrine, FiO_2 = fraction of inspired oxygen; norepi = norepinephrine; PaO_2 = partial pressure of oxygen.

a In non-ventilated subjects, a respiration score of 0 may be assigned.
b Values are with respiratory support.
c To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.
d Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/minute).
e To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

Source: Ferreira, 2001

Appendix 4 – Glasgow Coma Scale

Table 8: Glasgow Coma Scale

	Criterion	Rating	Score
Eye Opening	Open before stimulus	Spontaneous	4
	After spoken or shouted request	To sound	3
	After finger tip stimulus	To pressure	2
	No opening at any time, no interfering factor	None	1
	Closed by local factor	Non testable	NT
Verbal Response	Correctly gives name, place and date	Orientated	5
	Not orientated but communication coherently	Confused	4
	Intelligible single words	Words	3
	Only moans/groans	Sounds	2
	No audible response, no interfering factor	None	1
	Factor interfering with communication	Non testable	NT
Best Motor Response	Obey 2-part request	Obey commands	6
	Brings hand above clavicle to stimulus on head neck	Localizing	5
	Bends arm at elbow rapidly but features not predominantly abnormal	Normal flexion	4
	Bends arm at elbow, features clearly predominantly abnormal	Abnormal flexion	3
	Extends arm at elbow	Extension	2
	No movement in arms/legs, no interfering factor	None	1
	Paralysed or other limiting factor	Non testable	NT

In ventilated and sedated subjects, the GCS cannot be properly assessed, and a normal score of 15 could be used to complete the APACHE II and SOFA scores. If a reliable presedation score is available, it can be used.
Source: GCS-Assessment-Aid-English.pdf (glasgowcomascale.org)
Permission: https://www.glasgowcomascale.org/permissions/

Appendix 5 – Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Written informed consent to participate in the study will be obtained from all subjects before any protocol specific procedures are conducted. In the instance that subjects are unable to provide consent by themselves, consent must be obtained from the subject's legally authorized representative (according to local regulations). The ICF generated by the Sponsor or designee will be approved (along with the protocol) by the IRB/IEC.

Information about the study will be given to the subject both verbally and in writing. The written subject information sheet will explain the objectives of the study and its potential risk and benefits. The subject should have adequate time to read the information sheet and to ask the investigator

any questions. The investigator must be satisfied that the subject has understood the information provided before written consent is obtained. If there is any doubt as to whether the subject has understood the written and verbal information, the subject should not enter the study.

If a subject agrees to participate, he/she will be asked to sign and date the study ICF which will be retained by the investigator. A copy of the signed ICF will be given to the subject. The informed consent process must be documented in the subject's source documents. The original ICF must be retained by the investigator and made available for inspection by the study monitor.

Future Use of Subject Samples

No human samples will be stored for future biomedical research. Plasma samples for pharmacokinetic analysis will be stored for concentration assessments until the end of the study. Bacterial isolates (not human samples) will be stored until the completion of all regulatory requirements for registration.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in the electronic case report forms (eCRFs), study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject, or their legally authorized representative, must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her medical records may be examined by Sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Investigator Documentation Responsibilities

All individual, subject-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion. All data generated from external sources (e.g., central laboratory) and transmitted to the Sponsor or designee electronically will be integrated with the subject's eCRF data.

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Electronic Data Capture

The Sponsor will supply the investigational site with access to a web-based EDC computer system. Edit checks and data logic checks are at the point of entry and are validated according to company standard operating procedures. All data entered into the system are transferred to a secure database.

Access to the EDC system at the site, for vendors, at the Sponsor, and at the CRO is password protected. Study access is granted to site personnel only after they have been trained in the use of the EDC system at the investigational site.

The EDC system contains a system generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available at the investigator's site, at the CRO, and at the Sponsor.

Data entries made in the EDC screens should be completed within 5 days of the subject's study visit and must be supported by source documents maintained for all subjects enrolled in the study.

The data collection tool for this study will be the validated electronic system. Subject data necessary for analysis and reporting will be entered and transmitted via the electronic system. Clinical data management will be performed in accordance with applicable standards and data cleaning procedures. For data coding (e.g., adverse events [AEs], medication), internationally recognized and accepted dictionaries will be used.

After database lock has been declared all data will be delivered to the Sponsor.

Study Monitoring and Data Quality Assurance

The Sponsor or Sponsor's designee performs quality control and assurance checks on all clinical studies that it conducts. Before enrolling any subjects in this study, the Sponsor or Sponsor's designee and the investigator will review the protocol, the XNW4107 IB, the eCRF and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. The Sponsor's designee will monitor the conduct of the study at the site and will verify eCRF against source documents. Additionally, the Sponsor's designee will use automated validation programs to help identify missing data, selected protocol deviations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigator for resolution.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor or Sponsor's designee. Inspection of site facilities (e.g., pharmacy drug storage areas, laboratories, etc.) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Review of Source Documents

The investigator agrees that the study monitor (and other qualified personnel as appropriate) will be allowed to conduct site visits to the investigational facilities for the purpose of reviewing source records pertinent to the study. The investigator will make the study files available during monitoring visits. These files will also be available for inspection by representatives of the Sponsor, competent authorities, and/or the IEC/IRB. Subjects will not be identified by name on any of the study documents utilized by the Sponsor for their analysis, and confidentiality of information in medical records will be preserved. Every effort will be made to maintain the confidentiality of the subject unless disclosure is required by regulations.

Protocol Amendments

Any substantial amendments in the research protocol during the period, for which the IEC/IRB approval had already been given, will not be initiated without submission of an amendment for IEC/IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interest of preserving the safety of all subjects included in the trial.

Protocol Deviations

A protocol deviation is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IEC/IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Important protocol deviations, such as significant non-compliance or other serious unforeseen deviations deemed to invalidate the data collected in lieu of the purpose of the study will lead to exclusion of data from analysis. In case of non-protocol deviations, data will not be excluded from the data analysis.

All decisions regarding the type of deviations (important or non-important) will be made prior to commencing the final analysis on the final locked database. A listing of all subjects with protocol deviations will be maintained by the Sponsor and a listing of all important protocol deviations will be presented in the final study report.

Investigational sites will report protocol deviations to their IEC/IRB per institutional reporting requirements.

Change in Investigator

If any investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to the Sponsor or designee, IEC/IRB, or another investigator. The Sponsor or designee must be notified of and agree to the change. Regulatory agencies will be notified with the appropriate documentation.

Clinical Study Report

A clinical study report will be prepared following the completion of the study.

Confidentiality/Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Records Retention

Essential documents must be retained for longer than 5 years after completion of the study, 2 years after the final marketing authorization in an ICH region or until at least 2 years have elapsed since the discontinuation of clinical development of the study drug. If it becomes necessary for the Sponsor or the Competent Authority to review any documentation relating to the study, the investigator must permit access to such records.

Study files may be discarded upon written notification by the Sponsor. To avoid error, the investigator must contact the Sponsor before destroying any records or reports pertaining to the study, to ensure that retention is no longer required. Other source documents, such as subject's medical records, must be retained for the maximum period of time permitted by the hospital or institution and until such time when the investigator is informed by the Sponsor that there is no further need to do so.

In addition, in accordance with the investigator agreement, the Sponsor should be contacted if the site's principal investigator plans to leave the investigational site so that appropriate arrangements can be made.

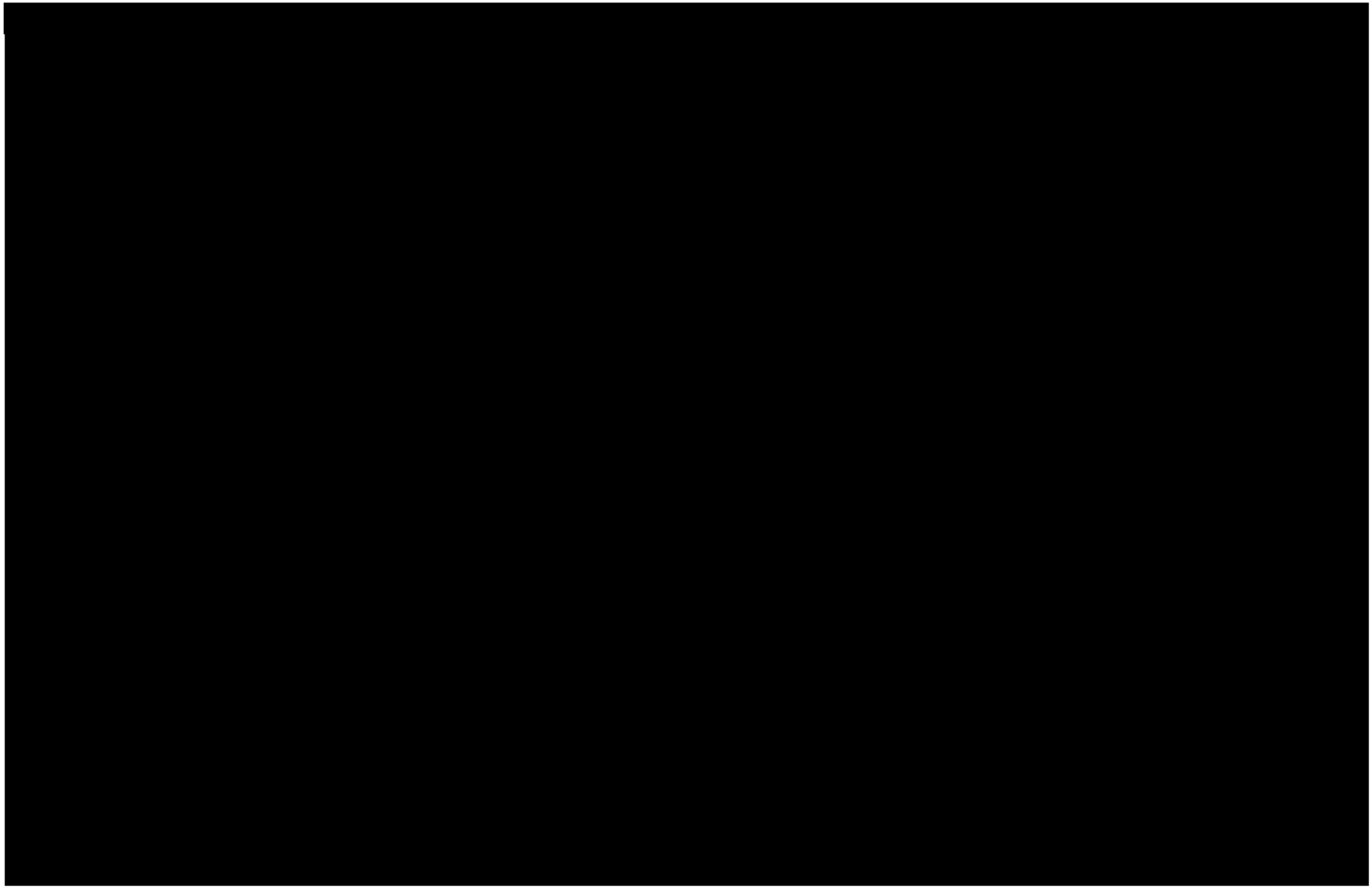
Publications

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur.

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except the investigator shall delete any confidential information from such proposed publications. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6 – Schedule of Assessments

Table 9: Schedule of Assessments



[redacted]

Appendix 7- Main study medical representative

Table 10: Main study medical representative

ROLE	NAME	CONTACT
Sponsor		
Sponsor's Medical Representative(China)	Jing Feng, Medical Monitor	E-mail:jing.feng@evopointbio.com phone: 0512-89162086
Sponsor's Medical Representative (Ex-China)	Cuiqiong Du, Medical Director	E-mail:tracy.du@evopointbio.com Phone: 14437660326
Clinical Research Organization (CRO)		
CRO Medical Monitor	Soto Norberto, Medical Director	E-mail:norberto.soto@labcorp.com Phone:1 609 212 7892