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Post-marketing study to assess the effectiveness and safety of RECARBRIO in Chinese adult patients with limited or no alternative treatment options for susceptible Gram-negative bacterial infections

SPONSOR
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(hereafter referred to as the Sponsor)
126 East Lincoln Ave
P.O. Box 2000
Rahway, New Jersey 07065
USA

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LIST OF ABBREVIATIONS

3GCRE	Third-Generation Cephalosporin-Resistant Enterobacterales
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
CAUTI	Catheter-Associated Urinary Tract Infection
CAZ-AVI	Ceftazidime-Avibactam
CHINET	China Antimicrobial Surveillance Network
CI	Confidence Interval
cIAI	Complicated Intra-Abdominal Infection
cm	Centimeter
CRAB	Carbapenem-Resistant Acinetobacter baumannii
CRE	Carbapenem-Resistant Enterobacterales
CRF	Case Report Form
CRKP	Carbapenem-Resistant Klebsiella pneumoniae
CRPA	Carbapenem-Resistant Pseudomonas aeruginosa
cUTI	Complicated Urinary Tract Infection
CVA	Costovertebral Angle
DCP	Data Curation Plan
DMP	Data Management Plan
DSUR	Development Safety Update Report
EC	Ethics Committee
EOT	End of Treatment
EOT-EAS	End of Treatment Effectiveness Analysis Set
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HABP/VABP	Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial
HAI	Hospital-Acquired Infection
hpf	High-Power Field
IAI	Intra-Abdominal Infection

ICU	Intensive Care Unit
IMP	Imipenemase
IQR	Interquartile Range
IRB	Institutional Review Board
kg	Kilogram
LPI	Last Patient In
LPLV	Last Patient Last Visit
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mmHg	Millimeter of Mercury
MSCC	Midstream Clean-Catch
NDM-1	New Delhi metallo-β-lactamase-1
NMPA	National Medical Products Administration
NSAR	Non-Serious Adverse Reaction
PBRER	Periodic Benefit Risk Evaluation Report
PI	Principal Investigator
PQC	Product Quality Complaint
PRS	Program Requirements and Specifications
PSUR	Periodic Safety Update Report
PT	Preferred Term
RDC	Remote Data Capture
RWS	Real-World Study
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure

SQI	Significant Quality Issue
TOC	Test of Cure
TOC-EAS	Test of Cure Effectiveness Analysis Set
UTI	Urinary Tract Infection
VIM	Verona integron-encoded metallo-β-lactamase
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

LIST OF DEFINITIONS

Baseline	The time window prior to the start of outcome follow-up, defined relative to the index date.
End-of-Treatment Visit	≤24 hours following the last dose of RECARBRIO for the index infection.
Favorable Clinical Response	Complete resolution or significant improvement of signs and symptoms of the index infection, as determined by the investigator.
Final Safety Follow-Up Visit	14 + 3 days following the last dose of RECARBRIO for the index infection.
Health Outcomes	Clinical events or outcomes which may be represented as diagnoses, treatments, or procedures (examples include syncope, disease progression, or hypoglycemia collected as study endpoints).
Index Date	The date of the first dose of RECARBRIO received for the index infection during the patient identification period.
Index Infection	The primary infection episode (HABP/VABP, cIAI, or cUTI, including pyelonephritis) for which the patient receives the first dose of RECARBRIO during the patient identification period. For patients with multiple concurrent infection sites, the investigator will identify one primary infection, which will be considered the index infection. Each patient may contribute only one index infection to the study.
Patient Identification Period	The period from 01-Dec-2024 through 31-Dec-2027 (the estimated date of last patient in) during which eligible patients will be identified. This end date may be extended based on enrollment status.
Test-of-Cure Visit	7 ± 2 days following the last dose of RECARBRIO for the index infection.

1 RESPONSIBLE PARTIES

Sponsor Study Lead	PPD Associate Principal Scientist, Epidemiology Asia-Pacific Unit, Biostatistics and Research Decision Sciences, MSD R&D (China) Co., Ltd. 42/F, Tower A, Phase III, Xujiahui Center, 183 Hongqiao Road, Xuhui District, Shanghai, China PPD
Supplier/Collaborator	TBD
Investigator(s)	TBD
Coordinating investigator for each country in which the study is to be performed	Not applicable
Other Contacts	PPD Scientist, Epidemiology Asia-Pacific Unit, Biostatistics and Research Decision Sciences, MSD R&D (China) Co., Ltd. 1-13F, Building 21, Rongda Road, Wangjing R&D Base, Zhongguancun Electronic Zone West Zone, Chaoyang District, Beijing 100012, China PPD

2 ABSTRACT

Title	Post-marketing study to assess the effectiveness and safety of RECARBRIO in Chinese adult patients with limited or no alternative treatment options for susceptible Gram-negative bacterial infections
Protocol Number / Version	7655A-035 / Version 1
Date Approved for the Most Recent Protocol Version	05-JUN-2026
Author	PPD Associate Principal Scientist, Epidemiology Asia-Pacific Unit, Biostatistics and Research Decision Sciences, MSD R&D (China) Co., Ltd. 42/F, Tower A, Phase III, Xujiahui Center, 183 Hongqiao Road, Xuhui District, Shanghai, China PPD PPD Scientist, Epidemiology Asia-Pacific Unit, Biostatistics and Research Decision Sciences, MSD R&D (China) Co., Ltd. 1-13F, Building 21, Rongda Road, Wangjing R&D Base, Zhongguancun Electronic Zone West Zone, Chaoyang District, Beijing 100012, China PPD

Rationale & Background	RECARBRIO (MK-7655A; imipenem/cilastatin/relebactam) was approved in China by the National Medical Products Administration (NMPA) on 01-Dec-2024 for the treatment of adult patients (≥18 years) with the following infections caused by designated susceptible Gram-negative microorganisms, as specified in the label: 1) hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP); 2) complicated urinary tract infections (cUTI, including pyelonephritis) in patients with limited or no alternative treatment options; and 3) complicated intra-abdominal infections (cIAI) in patients with limited or no alternative treatment options. In the approval letter, it was required that a post-marketing study be conducted in China to evaluate the effectiveness and safety of RECARBRIO in patients with limited or no alternative treatment options. To fulfill the post-marketing requirement, this real-world study (RWS) is designed to generate effectiveness and safety data for RECARBRIO in Chinese patients with limited or no alternative treatment options in real-world clinical settings.
Research Questions & Objectives	Primary objective: 1. To evaluate the effectiveness of RECARBRIO by estimating, separately, the proportion of patients with a favorable clinical response at the following visits: • Test of Cure (TOC; 7 ± 2 days following the last dose of RECARBRIO for the index infection), assessed in the TOC effectiveness analysis set (TOC-EAS) • End of Treatment (EOT; ≤24 hours following the last dose of RECARBRIO for the index infection), assessed in the EOT effectiveness analysis set (EOT-EAS) Secondary objective: 1. To evaluate the safety of RECARBRIO by describing the proportion of patients with one or more adverse events (AEs), adverse drug reactions (ADRs), serious AEs (SAEs), and serious ADRs (SADRs) from treatment initiation to 14 days following the last dose of treatment in the safety analysis set (SAS).

Study Design	This is a multicenter, non-interventional cohort study with a hybrid design incorporating both retrospective and prospective data collection. Data will be obtained primarily through chart review at participating sites using a standardized Case Report Form (CRF).
Population	The study population will consist of Chinese patients aged 18 years or older who have received at least one dose of RECARBRIO for HABP/VABP, cIAI, or cUTI (including pyelonephritis) with limited or no alternative treatment options. Limited or no alternative treatment options are defined as: 1) patients who have positive culture data obtained from the primary infection-site specimen, collected within 1 week prior to initiation of RECARBRIO, and with at least one identified Gram-negative pathogen that is non-susceptible to any one of the following antibiotics therapies: imipenem, meropenem, ertapenem (not considered for Pseudomonas species), biapenem, or ceftazidime-avibactam (CAZ-AVI); or 2) Patients with documented treatment failure of the current infection following prior imipenem, meropenem, ertapenem, biapenem, or CAZ-AVI therapy and with limited or no alternative treatment options based on investigators' assessment.
Variables	Exposure: Receipt of at least one dose of RECARBRIO during routine clinical practice. Primary outcomes: 1. Favorable clinical response to RECARBRIO for the index infection, assessed separately at the following visits: • TOC, assessed in the TOC-EAS • EOT, assessed in the EOT-EAS Secondary outcomes: 1. AEs, ADRs, SAEs, and SADRs assessed in the SAS at the following time points: • Retrospective data collection: From initiation of RECARBRIO treatment to 14 days following the last dose of treatment.

	• Prospective data collection: At initiation of RECARBRIO treatment, the EOT visit, the TOC visit, and the final safety follow-up visit (14+3 days following the last dose of RECARBRIO for the index infection). Other variables: Patient demographic, clinical, and microbiological characteristics, and treatment patterns.
Data Sources	Study data will be obtained primarily from routinely collected clinical information at participating sites. The main data sources will include medical records (electronic and/or paper), laboratory and microbiology reports, medication records related to RECARBRIO and concomitant systemic antibiotic therapy, and other relevant clinical documents, as available.
Study Size	All eligible patients at the participating sites will be identified and included during the patient identification period. Based on current estimates, approximately 140 patients are expected to be eligible for inclusion in the overall study population. The number of HABP/VABP patients should not exceed 30% of the overall study population, while patients with cIAI and cUTI (including pyelonephritis) should collectively account for at least 70%. The size of the overall study population reported in the final study report may be larger or smaller than estimated, depending on the actual circumstances.

Data Analysis	Results will be summarized using descriptive statistics. Study population characteristics, treatment patterns, and effectiveness outcomes of interest will be described using frequency and percentage distributions for categorical variables, and mean (standard deviation [SD]), median (interquartile range [IQR]), and range for continuous variables. Binomial confidence intervals will be calculated for estimates of effectiveness outcomes of interest. Safety data will be presented as numbers and percentages for reported AEs. The test of cure effectiveness analysis set (TOC-EAS) will consist of all eligible patients who have received at least 3 days of RECARBRIO for cIAI or cUTI (including pyelonephritis) with limited or no alternative treatment options and for whom the clinical response at the TOC visit is collected prospectively. The end of treatment effectiveness analysis set (EOT-EAS) will consist of all eligible patients who have received at least 3 days of RECARBRIO for cIAI or cUTI (including pyelonephritis) with limited or no alternative treatment options and for whom the clinical response at the EOT visit is collected prospectively or retrospectively. The safety analysis set (SAS) will consist of all eligible patients who have received at least one dose of RECARBRIO for HABP/VABP, cIAI, or cUTI (including pyelonephritis) with limited or no alternative treatment options. The SAS will be analyzed as two cohorts based on the timing of RECARBRIO treatment initiation relative to site initiation: • Retrospective cohort: patients who initiated RECARBRIO treatment prior to site initiation and who have at least one day of available medical records following the first dose of RECARBRIO • Prospective cohort: patients who initiated RECARBRIO treatment on or after site initiation

PAES INFORMATION

EU PAS Register No.	Study not registered
Active substance	Imipenem, Cilastatin, and Relebactam
Medicinal product:	Generic name: Imipenem, Cilastatin Sodium and Relebactam for Injection Trade name: RECARBRIO® MK number: MK-7655A
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder (MAH)	Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem, The Netherlands
Joint PASS	No
Country of study	China
Marketing authorisation holder including MAH Contact Person	PPD 42/F, Tower A, Phase III, Xujiahui Center, 183 Hongqiao Road, Xuhui District, Shanghai, China PPD Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem, The Netherlands
Sponsor Final Repository Date	05-JUN-2026
Date of Health Authority Approval of Protocol	Not applicable
Milestones:	
Start of data collection:	Q4 2026
End of data collection:	Q1 2028
Interim report(s) of study results:	Not applicable
Study progress report(s):	Not applicable
Final report of study results:	Q4 2028

3 PROTOCOL REVISION TABLE

Version No	Date	Section of Study Protocol	Revision Description	Reason	NIR DRC Approval Date
Original	None	None	None	None	05-MAY-2026

4 RATIONALE AND BACKGROUND

4.1 Background

Serious Gram-negative bacterial infections remain a major global concern due to their substantial clinical burden and the increasingly constrained therapeutic landscape. In the WHO 2024 Bacterial Priority Pathogens List, carbapenem-resistant Acinetobacter baumannii (CRAB), carbapenem-resistant Enterobacterales (CRE), and third-generation cephalosporin-resistant Enterobacterales (3GCRE) are classified as critical-priority pathogens, while carbapenem-resistant Pseudomonas aeruginosa (CRPA) is designated as high priority [1]. These classifications reflect the profound impact of antimicrobial resistance on the availability of last-line agents.

In China, national surveillance indicates a sustained and substantial burden of Gram-negative resistance. Long-term data from the China Antimicrobial Surveillance Network (CHINET) show CRAB consistently exceeding 60%, carbapenem-resistant Klebsiella pneumoniae (CRKP) exceeding 20% by the late 2010s, and CRPA decreasing gradually yet remaining around 20% [2]. The latest CHINET dataset (2025) reports CRAB at 76.4–76.5%, CRKP at 24.6–25.5%, and CRPA at 20.8–24.9% [2], underscoring the persistent challenge of securing effective therapy in Chinese healthcare settings.

These multidrug-resistant pathogens are commonly isolated from bloodstream, intra-abdominal, urinary tract, and respiratory tract infections, aligning with major clinical syndromes such as complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) [1] [3].

A cUTI is a symptomatic urinary tract infection (UTI) that occurs in association with anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, and/or other risk factors such as renal disease or other immunocompromising conditions, and includes upper tract infections such as pyelonephritis [4]. UTIs are common in both community and hospital settings [5]. In China, UTIs account for approximately 12% of all nosocomial infections [6], and a mean catheter-associated UTI (CAUTI) incidence of about 15% has been reported in Chinese studies [7]. The clinical burden of cUTI is substantial, with a large multicenter cohort reporting an overall cUTI mortality rate of 2.4% and a higher mortality rate of 4.5% among patients experiencing recurrent infections [8].

A cIAI is an intra-abdominal infection (IAI) that originates from a hollow viscus and extends beyond the organ of origin into the peritoneal cavity, causing localized or diffuse peritonitis [9] [10]. Overall, appendicitis is the most common cause of IAIs, occurring in approximately 7% of the population [11], and large epidemiological studies have identified IAI as the second most common source of sepsis, accounting for 22-32% of cases [12] [13]. The clinical consequences are severe, with global studies reporting an overall mortality rate for cIAI of approximately 9.2% [10]. In China, the clinical burden also appears substantial, with a 30-day all-cause mortality of 9.5% reported in a national multicenter surveillance of nosocomial IAIs [14], underscoring the serious impact of cIAI on adult patients.

HABP/VABP are major types of healthcare-associated infections (HAIs) in China. A national point-prevalence survey reported an overall HAI prevalence of 2.4%, with lower respiratory tract infections accounting for 48.4% of all HAIs, and HABP/VABP representing key subtypes within this category [15]. A large multicenter cohort study reported an overall incidence of HABP of 1.4%, increasing to 15.3% among patients in respiratory intensive care units [16]. The incidence of VABP in patients receiving mechanical ventilation has been reported to range from approximately 1.3 to 28.9 cases per 1,000 ventilator-days in Chinese studies [17]. These infections are associated with high mortality, with reported mortality rates ranging from approximately 13% to over 50%, and consistently higher mortality in VABP than in HABP in Chinese multicenter cohorts [18] [19] [20] [21] [22].

For these severe infections, the delayed availability of novel antibacterial agents in China has prolonged reliance on traditional therapies, such as complex polymyxin- or tigecycline-based combinations, which are limited by significant toxicity and a lack of robust efficacy data [23]. This highlights an urgent clinical need for safer and more effective targeted treatment options.

MSD has developed imipenem, cilastatin sodium and relebactam for injection, a fixed-dose combination known under the brand name RECARBRIO. RECARBRIO was approved in China by the National Medical Products Administration (NMPA) on 01-Dec-2024 for the treatment of patients 18 years of age and older with the following infections caused by the designated susceptible Gram-negative microorganisms, as specified in the label:

- HABP/VABP;
- cUTI (including pyelonephritis) in patients with limited or no alternative treatment options; and
- cIAI in patients with limited or no alternative treatment options.

4.2 Rationale

CCI [redacted]

Comprehensive clinical data, including the pivotal Phase III trial RESTORE-IMI 1 (for infections caused by imipenem-non-susceptible pathogens; NCT02452047), have demonstrated the efficacy and safety of RECARBRIO. However, for indications with limited treatment options (cUTI and cIAI), there are currently no specific clinical data in Chinese patients. Globally, published real-world evidence on RECARBRIO in cUTI and cIAI remains limited, and no relevant data are available for patients in Asia or specifically in China.

Real-world studies (RWS) can generate effectiveness and safety data in broader and more complex clinical settings. For example, in patients with limited treatment options (cUTI and cIAI), RWS can include those receiving combination therapy and those with underlying

conditions, who are often excluded from clinical trials. Such data can help better characterize the utilization, effectiveness, and safety of RECARBRIO in routine clinical practice.

To fulfill the post-marketing requirement, this RWS is proposed to generate the effectiveness and safety data for RECARBRIO in Chinese patients with cUTI and cIAI who have limited or no alternative treatment options in real-world settings. In addition, given the high proportion of multidrug resistance in HABP/VABP, including patients with HABP/VABP who have limited or no alternative treatment options will further enhance the generalizability of the findings and better support real-world clinical decision-making in China. This study will be designed in accordance with relevant regulatory and methodological guidelines to ensure scientific rigor.

5 RESEARCH QUESTION AND OBJECTIVES

5.1 Primary Objective

1. To evaluate the effectiveness of RECARBRIO by estimating, separately, the proportion of patients with a favorable clinical response[1] at the following visits:

    - Test of Cure (TOC; 7 ± 2 days following the last dose of RECARBRIO for the index infection), assessed in the TOC effectiveness analysis set (TOC-EAS; Section 6.9.1.2)

    - End of Treatment (EOT; ≤24 hours following the last dose of RECARBRIO for the index infection), assessed in the EOT effectiveness analysis set (EOT-EAS; Section 6.9.1.3)

5.2 Secondary Objective

2. To evaluate the safety of RECARBRIO by describing the proportion of patients with one or more adverse events (AEs), adverse drug reactions (ADRs), serious AEs (SAEs), and serious ADRs (SADRs) from treatment initiation to 14 days following the last dose of treatment in the safety analysis set (SAS; Section 6.9.1.4).

[1] Favorable clinical response (i.e., clinical cure) is defined as the complete resolution or significant improvement of signs and symptoms of the index infection, as determined by the investigator (Section 6.3.2.1).

6 RESEARCH METHODS

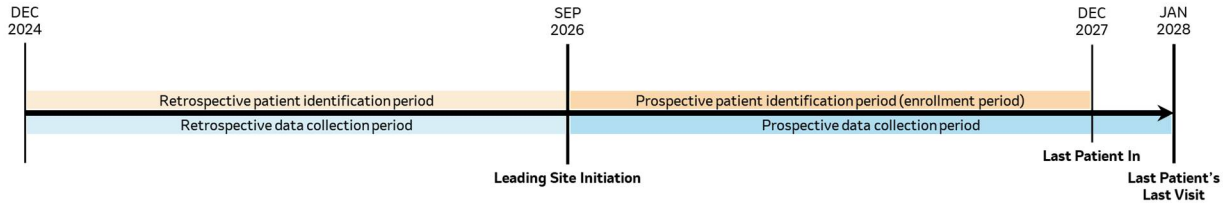
6.1 Study Design

This is a multicenter, non-interventional cohort study with a hybrid design incorporating both retrospective and prospective data collection. The study period is planned to span from 01-Dec-2024 to 31-Jan-2028, including both retrospective and prospective patient identification and data collection, which are distinguished by the site initiation date at each participating site (Figure 1). Data will be primarily obtained through chart review using a standardized Case Report Form (CRF). All patients will receive RECARBRIO as part of routine clinical practice.

The study population will consist of Chinese patients aged 18 years or older who have received at least one dose of RECARBRIO for HABP/VABP, cIAI, or cUTI (including pyelonephritis) with limited or no alternative treatment options and meet all study inclusion and exclusion criteria. Patients will be followed from receipt of the first dose of RECARBRIO for the index infection, defined as the primary infection episode (HABP/VABP, cIAI, or cUTI, including pyelonephritis) for which the patient receives the first dose of RECARBRIO, through the defined assessment window.

The study will evaluate the real-world effectiveness of RECARBRIO based on favorable clinical outcomes and will assess its safety by summarizing AEs, ADRs, SAEs, and SADRs. In addition, patient demographic, clinical, and microbiological characteristics, and treatment patterns will be described. Study data will be abstracted by qualified designees from multiple data sources within participating sites, such as medical records, laboratory reports, medication records, and other relevant clinical documentation, as available.

Figure 1 Study timeline for patient identification and data collection



Note: The leading site initiation date is shown as an example. Actual timelines will be determined by the initiation date of each participating site.

6.2 Setting

6.2.1 Study Population

The study population will consist of Chinese patients aged 18 years or older who have received at least one dose of RECARBRIO for HABP/VABP, cIAI, or cUTI (including pyelonephritis) with limited or no alternative treatment options during the patient identification period (Section 6.2.4.1) and meet all study inclusion criteria and none of the exclusion criteria.

6.2.2 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designees to ensure that the patient qualifies for the study.

Inclusion Criteria

1. Chinese and resident of China.
2. Has received at least one dose of RECARBRIO for the treatment of the current index infection.
3. At least 18 years of age on the day of RECARBRIO treatment initiation.
4. Diagnosed with HABP/VABP, cIAI, or cUTI (including pyelonephritis) with limited or no alternative treatment options. Limited or no alternative treatment options are defined as one of the following:
    a. Patients who have positive culture data obtained from the primary infection-site specimen, collected within 1 week prior to initiation of RECARBRIO, and with at least one identified Gram-negative pathogen that is non-susceptible to any one of the following antibiotics therapies: imipenem, meropenem, ertapenem (not considered for Pseudomonas species), biapenem, or ceftazidime-avibactam (CAZ-AVI).
    b. Patients with documented treatment failure of the current infection following prior imipenem, meropenem, ertapenem, biapenem, or CAZ-AVI therapy and with limited or no alternative treatment options based on investigators' assessment.

Exclusion Criteria

1. Unable to provide written informed consent if required by the ethics committee.
2. Participating in any interventional clinical trial during the patient's data collection period.
3. Pregnant or breastfeeding during RECARBRIO treatment.
4. Prior enrollment in this study (each patient may only be enrolled once).
5. Has an infection in which any of the causative pathogens are imipenem-resistant Acinetobacter spp. or suspected Class B metallo-beta-lactamase-producing bacteria (including New Delhi metallo-β-lactamase-1 [NDM-1], imipenemase [IMP], or Verona integron-encoded metallo-β-lactamase [VIM]-containing strains).
6. Hypersensitive to the active substances or any of the inactive excipients of RECARBRIO.
7. Concurrent infection that would interfere with evaluation of response to the study antibiotics, including any of the following: endocarditis, osteomyelitis, meningitis, prosthetic joint infection, active pulmonary tuberculosis or disseminated fungal infection.

6.2.3 Study Sites

Hospitals in China where RECARBRIO is available and has demonstrated high patient utilization during the study period will be prioritized for inclusion. Key considerations for site selection include availability of RECARBRIO, sufficient volume of potentially eligible patients, principal investigator's (PI) willingness to participate, completeness of medical records for key study variables, and favorable operational feasibility assessment. Approximately 10 sites are expected to be included, with patient identification and

enrollment focusing on departments where RECARBRIO is commonly used, such as ICU, Urology, Nephrology, and Surgery.

6.2.4 Study Period

The overall study period will begin on 01-Dec-2024, the date of RECARBRIO's approval in China, and will end on 31-Jan-2028, the estimated date of the last patient's last visit (LPLV). The actual study period may be adjusted based on real-world timing of data availability and completion of routine clinical follow-up.

The study will incorporate both retrospective and prospective data collection components. Retrospective data will be collected from 01-Dec-2024 through the date of site initiation at each participating site. Prospective data will be collected from the date of site initiation through LPLV.

6.2.4.1 Patient Identification Period

Eligible patients will be identified from 01-Dec-2024 through 31-Dec-2027, the estimated date of the last patient in (LPI). This end date may be extended based on enrollment status.

The patient identification period will include both retrospective and prospective components. For retrospective identification, patients who initiated RECARBRIO treatment prior to their site initiation and who meet the eligibility criteria will be identified through review of existing medical records. For prospective identification, patients who initiate RECARBRIO treatment on or after their site initiation as part of routine clinical practice and who meet the eligibility criteria will be consecutively identified.

Patients identified retrospectively or prospectively will be enrolled in accordance with the informed consent requirements and procedures described in Section 7.1, from their site initiation date through the date of LPI.

Identification and enrollment of patients will not alter or influence prescribing decisions, which will remain at the discretion of the treating physician.

6.2.4.2 Index Date

The index date for each patient is defined as the date of the first dose of RECARBRIO received for the index infection during the patient identification period. For patients identified retrospectively, the index date will be determined from existing medical records. For patients identified prospectively, the index date will be recorded at the time of the first dose of RECARBRIO as part of routine clinical practice.

The index infection is defined as the primary infection episode (HABP/VABP, cIAI, or cUTI, including pyelonephritis) for which the patient receives the first dose of RECARBRIO during the patient identification period (Section 6.2.4.1). For patients with multiple concurrent infection sites, the investigator will identify one primary infection, which will be

considered the index infection. Each patient may contribute only one index infection to the study.

6.2.4.3 Follow-up Period

Patients will be followed from the index date until death or the last documented clinical encounter or study-related contact within the study period, whichever occurs first. In the absence of a recorded death, the date of the last documented clinical encounter or study-related contact will define the end of follow-up. For the purposes of this study, study-related contacts are defined as any documented contacts initiated by the study team for the purposes of this study that are relevant to the index infection or safety assessment, such as telephone follow-up. All study-related information documented in the medical record or obtained through such study-related contacts during this period will be collected.

Within the overall follow-up period, the following assessment time points are of interest, as applicable:

- EOT visit: ≤24 hours following the last dose of RECARBRIO for the index infection.
- TOC visit: 7 ± 2 days following the last dose of RECARBRIO for the index infection.
- Final safety follow-up visit: 14 + 3 days following the last dose of RECARBRIO for the index infection.

For patients who initiated RECARBRIO treatment for the index infection prior to their site initiation, but whose follow-up extends beyond site initiation, pre-initiation data will be collected retrospectively through review of existing medical records, and post-initiation data, which may include EOT, TOC, and final safety follow-up visits as applicable, may be collected prospectively.

6.3 Variables

6.3.1 Exposure

Exposure is defined as receipt of at least one dose of RECARBRIO as part of routine clinical practice for the treatment of HABP/VABP, cIAI, or cUTI (including pyelonephritis) in patients with limited or no alternative treatment options. All treatment decisions are made by the treating physician in accordance with the approved labeling and local clinical practice.

The treatment period is defined as the time from the index date (Section 6.2.4.2) to the last dose of RECARBRIO for the index infection. RECARBRIO is administered via intravenous infusion as per the approved labeling. The following treatment-related information will be collected where available:

- Dates of RECARBRIO administration
- Dose and dosing frequency (including any dose adjustments)
- Changes in dosing regimen (dose reduction, increase, interruption, or discontinuation) and corresponding reasons, if applicable
- Concomitant systemic antibiotic therapy (drug name and dates of use), if any

- Treatment setting, where relevant (e.g., ICU vs non-ICU)
- Other relevant treatment details, as available

The following variables will be derived to describe RECARBRIO treatment patterns:

- Treatment duration (days)
- Treatment modality (monotherapy vs combination therapy):
  - Monotherapy: RECARBRIO without concomitant use of any other systemic antibiotic providing Gram-negative coverage. Concomitant use of antibiotics primarily for Gram-positive or anaerobic coverage, including metronidazole for cIAI, will still be classified as monotherapy
  - Combination therapy: RECARBRIO plus other systemic antibiotic(s) providing Gram-negative coverage, with overlapping treatment dates
- Dose adjustment (yes vs no)
- Treatment discontinuation (yes vs no)

6.3.2 Outcomes

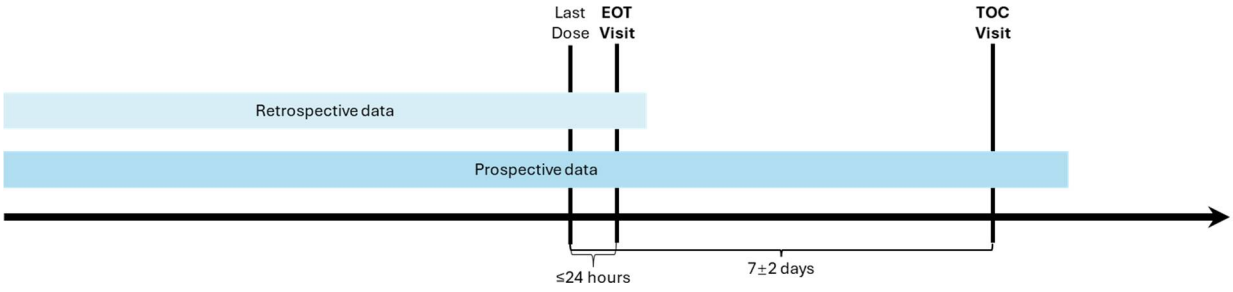
If any health outcomes are herein described, collected per the protocol, they will be summarized in the final study report in addition to being reported in real-time as individual AEs if the criteria in section 8 are met. Refer to Section 8 for AE reporting requirements and procedures.

6.3.2.1 Primary Outcomes: Favorable Clinical Response

The primary outcomes are favorable clinical response (clinical cure) to RECARBRIO for the index infection, assessed separately at the TOC and EOT visits, in the overall study population who have received at least 3 days of RECARBRIO for the treatment of cIAI or cUTI (including pyelonephritis) with limited or no alternative treatment options.

Clinical response will be determined by the investigator separately at EOT based on retrospectively and prospectively collected data, and at the TOC visit based on prospectively collected data only, when available, as part of routine clinical practice (Figure 2).

Figure 2 Clinical Response Assessment Based on Retrospective and Prospective Data



Abbreviations: EOT, end of treatment; TOC, test of cure.

Clinical responses will be classified as follows:

- Favorable clinical response (clinical cure): Complete resolution or significant improvement of signs and symptoms of the index infection.
- Clinical failure: Lack of improvement or progression of signs and symptoms of the index infection, or development of new signs or symptoms consistent with ongoing or recurrent index infection, or death considered to be related to the index infection.
- Indeterminate: Clinical response cannot be determined due to insufficient or missing data for any reason, or death considered to be unrelated to the index infection or of unknown cause.

Presence or absence of specific clinical signs and symptoms relevant for each infection site of interest will be recorded, including the following:

cIAI:

- Fever or hypothermia (record the highest or lowest body temperature observed during the assessment period)
- Abdominal pain or flank pain, or pain caused by cIAI that is referred to another anatomic area such as back or hip
- Tenderness to palpation, rebound tenderness, guarding mass, ascites, ileus, bowel sounds, need for enteral feeding
- Nausea or vomiting
- White blood cell count elevated beyond the upper limit of the normal laboratory range or the proportion of band forms of the with blood cell differential count beyond the upper limit of the normal laboratory range

cUTI:

- Fever (record the highest body temperature observed during the assessment period)
- Chills or rigors
- Flank pain or costovertebral angle (CVA) tenderness on physical examination
- Dysuria, urinary frequency, suprapubic or pelvic pain, or urinary urgency
- Nausea or vomiting
- Pyuria determined by a midstream clean-catch (MSCC) or catheterized urine specimen with ≥10 white blood cells (WBCs) per high-power field (hpf) on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine (a urine dipstick may be employed)

Other clinical signs and symptoms relevant for each infection site of interest as determined by the investigator.

6.3.2.2 Secondary Outcomes: Safety Outcomes

The secondary outcomes are safety outcomes, which will be evaluated in the overall study population by summarizing AEs, ADRs, SAEs, and SADRs.

AEs, ADRs, SAEs, and SADRs will be determined by the investigator from the index date to 14 days following the last dose of RECARBRIO for the index infection:

- For patients whose RECARBRIO treatment for the index infection and the subsequent 14 days following the last dose of treatment are completed prior to their site initiation, safety outcomes will be collected retrospectively from existing medical records.
- For patients who initiate RECARBRIO prior to their site initiation, but whose treatment and/or safety follow-up extend beyond site initiation, safety outcomes will be collected retrospectively for the pre-initiation period and prospectively from the time of enrollment, including an assessment at enrollment and at subsequent follow-up time points, which may include, but are not limited to, the EOT visit, TOC visit, and final safety follow-up visit, as applicable.
- For patients who initiate RECARBRIO on or after site initiation, safety outcomes will be collected prospectively at the index date, the EOT visit, the TOC visit, and the final safety follow-up visit, and from any additional safety-related information documented in the medical records.

The evaluation of each AE will follow the definitions described in Section 8.2 for AEs (Section 8.2.1), ADRs (Section 8.2.2), SAEs and SADRs (Section 8.2.3 and Annex 3), non-serious ADRs (Section 8.2.4), and causality assessment (Section 8.2.9 and Annex 4).

6.3.3 Covariates

The following characteristics will be collected, where available. The variables may be refined and will be finalized in the CRF.

Demographics:

- Age at index date (years): Derived from Date of Birth
- Sex: male / female
- Height (cm)
- Weight (kg)
- BMI (kg/m^2): Derived from Height and Weight
- Geographic region: Derived from Province of Residence
- National basic medical insurance coverage: yes / no / unknown

Clinical characteristics:

- Index infection type: HABP/VABP, cIAI, or cUTI (including pyelonephritis)
- Presence of bacteremia at baseline: yes / no / unknown
- Respiratory rate at baseline (breaths/min)
- Systolic and diastolic blood pressure at baseline (mmHg)
- Heart rate at baseline (beats/min)
- Body temperature at baseline (°C)
- Status of consciousness at baseline (e.g., alert, drowsy, stupor, coma; as recorded in the medical records)

- Mechanical ventilation at baseline: yes / no / unknown
- ICU admission at baseline: yes / no / unknown
- Renal replacement therapy at baseline: yes / no / unknown

Microbiological characteristics:

- Microbiological test results at baseline, including but not limited to the pathogen(s) isolated, specimen source, and antimicrobial susceptibility results. For patients with cUTI whose clinical response at EOT is classified as clinical failure (Section 6.3.2.1), microbiological test results through EOT will also be included.

Laboratory values:

- Serum creatinine or creatinine clearance at baseline, where available

Medical history and treatment history:

- Comorbidities (e.g., diabetes, chronic kidney disease, chronic liver disease, malignancy, immunocompromised status)
- History of systemic antibiotic therapy: Collected within 14 days prior to the index date
- History of other relevant medications: Collected within 7 days prior to the index date

6.4 Data Sources

Study data will be obtained primarily from routinely collected clinical information at participating sites. The main data sources will include medical records (electronic and/or paper), laboratory and microbiology reports, medication records related to RECARBRIO and concomitant systemic antibiotic therapy, and other relevant clinical documents, as available.

To enhance data consistency and quality, data abstraction will be performed by qualified designees using a standardized CRF with predefined variable definitions and data entry instructions. Data quality checks and programming validation procedures will be applied as described in subsequent sections.

6.5 Study Procedures

This is a multicenter, non-interventional cohort study with a hybrid design incorporating both retrospective and prospective data collection. All patients will receive RECARBRIO as part of routine clinical practice at the discretion of the treating physician, and the study will not mandate any additional diagnostic or therapeutic interventions. Study data will be obtained primarily from routine clinical documentation through chart review using a standardized CRF, with qualified designees abstracting information from multiple site data sources (Section 6.4).

For patients with retrospective data collection only, RECARBRIO treatment for the index infection and the subsequent 14 days following the last dose of treatment will have been fully completed prior to their site initiation. All study data will be obtained exclusively from

existing medical records and other relevant source documents at the site. No study-related contacts will be performed for these patients.

For patients with prospective data collection (with or without an initial retrospective chart review), follow-up will extend from the first dose of RECARBRIO for the index infection through predefined assessment windows. Prospective data will be derived mainly from routine clinical practice and may be supplemented, when necessary, by limited study-related contacts (e.g., telephone follow-up). The timing of study procedures and assessments for these patients is summarized in (Table 1). Specific visit time points are not prescribed by the protocol.

Table 1 Operational Study Diagram for Patients with Prospective Data Collection

Study Procedures	**V1: Enrollment[a]**	**V2: EOT**	**V3: TOC**	**V4: Final Safety Follow-up**
Visit window (relative, non-prescriptive)	On or after site initiation	≤24 hours after last dose	7 ± 2 days after last dose	14 + 3 days after last dose
Informed consent	X			
Inclusion/Exclusion criteria	X			
Baseline characteristics	X			
Prior medications and treatments	X			
Concomitant medications and treatments	X	X	X	X
RECARBRIO treatment information	X	X		
Clinical assessment and response evaluation	X	X[b]	X[b]	
Safety assessment (AEs, ADRs, etc.)	X	X	X	X

Abbreviations: ADR, adverse drug reaction; AE, adverse event; EOT, end of treatment; TOC, test of cure.

[a] Enrollment (V1) occurs on or after site initiation and represents the first study-related documentation for patients with prospective data collection. The index date is defined as the date of first RECARBRIO dose for the index infection and may occur before or after site initiation. If Enrollment falls within the EOT, TOC, or final safety follow-up window for a patient, assessments for Enrollment and the corresponding visit may be combined.

[b] Only for eligible patients who have received at least 3 days of RECARBRIO for cIAI and cUTI (including pyelonephritis) with limited or no alternative treatment options.

Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. Any evaluations or testing conducted as part of usual care, including those prompted by safety concerns, may be documented in the medical

record. The protocol does not mandate any additional procedures beyond standard clinical practice.

6.5.1 Administrative Procedures

Informed Consent: Informed consent will be obtained, or a waiver of consent will be applied, in accordance with the requirements and procedures detailed in Section 7.1 and as approved by the IRB/EC at each site.

Inclusion/Exclusion Criteria: The investigator or qualified designees will review the inclusion and exclusion criteria (Section 6.2.2) to confirm that the patient is eligible for the study. Eligibility will be documented in the CRF.

Assignment of Patient Identification Number: Each enrolled patient will be assigned a unique patient identification number at the time of enrollment, which will be used on all study documents and in the CRF.

Source Documentation and Data Entry: Study data will be abstracted from source documents and entered into the CRF by qualified designees, in line with the study procedures and overall data collection schedule summarized above.

6.6 Study Size

As this is a non-interventional study without a control group, hypothesis tests and power calculations will not be utilized. All eligible patients at participating sites will be identified and included during the patient identification period (Section 6.2.4.1).

Based on estimates, approximately 140 patients are expected to be eligible for inclusion in the overall study population. The number of HABP/VABP patients should not exceed 30% of the overall study population. Patients with cIAI and cUTI should collectively account for at least 70% of the overall study population. The overall study population in the final study report may be larger or smaller than the estimation, depending on the actual circumstances.

The study size estimation is based on projected market supply, clinical experience, and feasibility assessments. Specifically,

- It is estimated to include approximately 10 sites with potentially higher usage of RECARBRIO and a larger estimated number of patients with the target indications, where approximately 10% of the total supply of RECARBRIO in China will be concentrated.
- An estimated 15% of the patients will meet the definition of having limited or no alternative treatment options for HABP/VABP, cIAI, or cUTI (including pyelonephritis).
- It is estimated that 70% of potential target patients are expected to sign the informed consent form, and almost all these patients will receive at least one dose of RECARBRIO, comprising the overall study population.

6.7 Data Management

All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance of data have been assessed to meet the minimum requirements for all study objectives.

If this study has been outsourced, the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Data Management Software and Hardware:

Study data will be managed using Oracle Clinical Remote Data Capture (RDC) Onsite Version 4.6.2. Statistical analyses may be conducted using SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina) and/or R (latest version).

Description of Data Preparation and Methods for Data Retrieval and Collection:

Data for this study will be obtained primarily from routine clinical practice and abstracted from multiple data sources within participating sites, including but not limited to medical records, laboratory reports, medication records, and other relevant clinical documentation. Outcome data, including clinical response as well as safety outcomes, will be retrieved based on investigators' clinical assessments. A CRF will be used to capture all data. A stand-alone Data Management Plan (DMP) with or without a stand-alone Data Curation Plan (DCP) will be developed to describe detailed procedures for data retrieval, preparation, cleaning, and quality checks.

6.8 Programming Quality

This study will incorporate the following quality checks for data analysis and reporting programming:

- Creating a Program Requirements and Specifications document (PRS).
- Developing and testing of statistical programs which includes ensuring the programs run successfully and all output are reviewed to ensure they meet the criteria included in the PRS. This includes validating that all inputs (metadata or parameter values) are correctly specified in the programs and are consistent with the PRS.
- For statistical programs and code supporting analysis datasets, primary objectives and protocol specific analysis, independent double programming will be conducted by a second programmer. After programming is completed, the programs and results of the second programmer will be compared to those of the first programmer to ensure

consistency. If discrepancies are found, the programmers will discuss and repeat steps until consistency is achieved.

- For statistical programs and code supporting secondary objectives and baseline characteristics analysis, independent review and testing will be conducted by a second programmer to ensure that the inputs and outputs of the programs created by the first programmer meet the documented PRS. This includes the following 2 activities:
  - Review of code to ensure the program aligns with the PRS.
  - Execution of the code and review of results for some or all scenarios.

  And may include the following activity:
  - Parallel programming of a small piece of critical code
- Review of outputs/results to ensure accuracy and format of each deliverable.

6.9 Data Analysis

Unless otherwise specified, all analyses will be descriptive in nature, and no formal hypothesis testing will be performed. Patient attrition (e.g., numbers eligible and included in each analysis set), patient characteristics, treatment patterns, and effectiveness outcomes of interest will be described using frequency and percentage distributions for categorical variables, and mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum for continuous variables. Binomial confidence intervals (CIs) will be calculated for selected proportions. Safety data will be presented as numbers and percentages of patients with reported safety outcomes. Medical histories and safety data will be coded and reported using the Medical Dictionary for Regulatory Activities (MedDRA), and medications will be coded and reported using the World Health Organization Drug Dictionary (WHODD). All analyses will be based on available data. For the primary effectiveness outcomes, missing clinical response data for any reason will be classified as "Indeterminate" as defined in Section 6.3.2.1.

Results will be summarized in tables, figures, and listings.

A stand-alone Statistical Analysis Plan (SAP) will be developed to provide detailed specifications of the analyses, including shells for tables, figures, and listings, which will be finalized before database lock.

6.9.1 Analysis Sets

6.9.1.1 Overall Study Population

The overall study population will consist of all eligible patients who are included in the study (Section 6.2.1).

6.9.1.2 Test of Cure Effectiveness Analysis Set

The Test of Cure Effectiveness Analysis Set (TOC-EAS) will consist of all eligible patients who have received at least 3 days of RECARBRIO for cIAI and cUTI (including pyelonephritis) with limited or no alternative treatment options and for whom the clinical response at the TOC visit is collected prospectively.

6.9.1.3 End of Treatment Effectiveness Analysis Set

The End of Treatment Effectiveness Analysis Set (EOT-EAS) will consist of all eligible patients who have received at least 3 days of RECARBRIO for cIAI or cUTI (including pyelonephritis) with limited or no alternative treatment options and for whom the clinical response at the EOT visit is collected prospectively or retrospectively.

6.9.1.4 Safety Analysis Set

The Safety Analysis Set (SAS) will consist of all eligible patients who have received at least one dose of RECARBRIO for HABP/VABP, cIAI, or cUTI (including pyelonephritis) with limited or no alternative treatment options. The SAS will be analyzed as two cohorts based on the timing of RECARBRIO treatment initiation relative to site initiation:

- Retrospective cohort: patients who initiated RECARBRIO treatment prior to site initiation and who have at least one day of available medical records following the first dose of RECARBRIO
- Prospective cohort: patients who initiated RECARBRIO treatment on or after site initiation

6.9.2 Analysis of Baseline Characteristics

Patient demographic, clinical, and microbiological characteristics, as described in Section 6.3.3, will be summarized descriptively, where applicable, for the following analysis populations:

- Overall study population
- EOT-EAS.

In addition, the length of overall follow-up (Section 6.2.4.3) will be summarized descriptively for each of these groups.

6.9.3 Analysis of Treatment Patterns

Treatment patterns (Section 6.3.1) will be summarized descriptively for the overall study population.

6.9.4 Primary Analyses: Favorable Clinical Response

The favorable clinical response (clinical cure; Section 6.3.2.1) will be summarized separately at TOC, depending on data availability, and at EOT.

The favorable clinical response at TOC will be summarized in the TOC-EAS, depending on data availability. If the TOC data are deemed insufficient, defined as the proportion of patients with “indeterminate” clinical responses at TOC due to missing TOC assessments exceeding 16%, the clinical response at TOC will not be analyzed.

For the TOC visit, the number and proportion of patients with a favorable clinical response will be reported, with 95% exact binomial (Clopper-Pearson method) CIs. The proportion of patients with a favorable clinical response will be calculated as:

- *Proportion with favorable clinical response at the TOC visit (%) = (Number of patients in the TOC-EAS with a favorable clinical response at the TOC visit / Total number of patients in the TOC-EAS) × 100*

The favorable clinical response at EOT will be summarized in the EOT-EAS. The number and proportion of patients with a favorable clinical response will be reported, with 95% exact binomial (Clopper-Pearson method) CIs. The proportion of patients with a favorable clinical response will be calculated as:

- *Proportion with favorable clinical response at the EOT visit (%) = (Number of patients in the EOT-EAS with a favorable clinical response at the EOT visit / Total number of patients in the EOT-EAS) × 100*

For favorable clinical response at the TOC and EOT visits separately, considering that a high proportion of indeterminate responses may result from missing follow-up, sensitivity analyses may be conducted to assess the robustness of the primary analysis. The specific approach will be pre-specified in the SAP.

In addition, the above analyses may also be conducted in the following subgroups, depending on data availability:

- Data collection method (e.g., any retrospective vs prospective only)
- Infection type (cIAI vs cUTI, including pyelonephritis)
- Baseline resistance phenotype (e.g., carbapenem-resistant vs non-carbapenem-resistant Gram-negative pathogens)
- ICU admission at baseline (ICU vs non-ICU)
- Other clinically relevant subgroups, as pre-specified in the SAP

6.9.5 Secondary Analyses: Safety Outcomes

AEs, ADRs, SAEs, and SADRs (Section 6.3.2.2) will be summarized separately for the retrospective and prospective cohorts of the SAS as the number and percentage of patients experiencing at least one event of each type from the index date to 14 days following the last dose of RECARBRIO for the index infection, by system organ class (SOC) and preferred term (PT).

Safety analyses for patients with any special situation (Section 8.2.5) will be conducted independently and presented separately, if applicable.

6.10 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), Good Pharmacovigilance Practices (GVP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP and GVP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

6.11 Limitations of the Research Methods

This is a multicenter, non-interventional cohort study with a hybrid design incorporating both retrospective and prospective data collection. While this approach provides a comprehensive understanding of treatment patterns and outcomes in real-world clinical practice, several limitations should be considered when interpreting the findings.

First, treatment with RECARBRIO is not randomized. The decision to initiate therapy, as well as the timing and duration of treatment, is made by physicians as part of routine clinical practice. This may lead to channeling of RECARBRIO to patients with specific clinical or socioeconomic characteristics and may introduce the possibility of selection bias.

Second, as the study is primarily descriptive and does not include formal hypothesis testing or prespecified multivariable adjustment to control for potential confounding, any observed differences between subgroups should be understood as descriptive associations rather than causal inferences.

Third, the combination of retrospective and prospective data collection may lead to heterogeneity in data completeness and quality. For retrospective cases, some historical clinical information may be missing or incompletely documented, and follow-up information after the index hospitalization or visit may be limited. For prospective cases, outcomes and AEs will be captured through routine clinical visits and, when necessary, supplemented by telephone follow-up. Although these approaches are designed to reflect real-world practice, they may lead to incomplete capture of treatment exposure or outcomes in some patients, potentially resulting in under- or overestimation of effectiveness and safety outcomes. Efforts will be made to obtain key outcome information through available medical records and study-related follow-up contacts; however, some degree of missing data and loss to follow-up cannot be completely avoided.

Finally, the participating sites are considered to be higher-level hospitals where RECARBRIO is available for patients with HABP/VABP, cIAI, or cUTI (including pyelonephritis) who have limited or no alternative treatment options. Clinical practice patterns, patient characteristics, access to care, and local pathogen and resistance profiles may vary across institutions or regions, which may influence the generalizability of results. Additionally, the overall sample size and the number of patients within certain subgroups may be limited, which could reduce the precision of some estimates and result in wider confidence intervals.

In consideration of the above potential limitations, several measures will be implemented to support appropriate interpretation of the study findings. Patient demographic, clinical, and microbiological characteristics will be systematically collected and descriptively summarized to provide a clear profile of the overall study population and subpopulations of interest. Outcome analyses will primarily be descriptive, with subgroup results presented to illustrate observed patterns rather than to support causal inference. To address potential variability in data completeness and quality, key variables and outcomes will be predefined, and data collection procedures for prospectively enrolled patients will be standardized to enhance consistency and reduce information bias. Data quality and completeness will be monitored, and missing data patterns will be reported transparently to enable appropriate interpretation of the findings. In addition, results from smaller subgroups will be interpreted cautiously, with explicit acknowledgement of limitations in generalizability and estimation precision. These planned measures are intended to mitigate inherent methodological constraints while preserving the real-world nature of the evidence to be generated by this study.

6.12 Other Aspects

Not applicable.

7 PROTECTION OF HUMAN SUBJECTS

7.1 Informed Consent

This study will require participant informed consent for patients from whom any prospective data are collected after site initiation (e.g., outcomes of interest obtained at predefined follow-up visits or through study-related follow-up contacts). For patients whose data are collected exclusively retrospectively (i.e., all study data for the index infection are obtained from existing medical records prior to site initiation and no additional contact with the patient is needed), a waiver of informed consent may be requested from the IRB/EC in accordance with applicable laws and regulations.

This study will require participant IRB/EC review. Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. Whenever feasible, study files should be coded and stripped of personal identifiers, and code keys should be stored separately from study files.

The informed consent will adhere to IRB/EC requirements, applicable laws and regulations and Sponsor requirements.

The initial informed consent form, any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB/EC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

8 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study being conducted within routine medical practice, which includes primary data collection and use of secondary data collected for other purposes. All directions for medication usage are at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

8.1 Adverse Event and Product Quality Complaint Reporting

8.1.1 Investigator Responsibility

Primary Data Collection (prospective collection of study-specific data through study-related contacts [e.g., telephone follow-up] after site initiation): AEs and PQCs are not actively solicited in this study, however, if adverse events (AEs) or product quality complaints (PQCs) are identified following use of RECARBRIO or any other Sponsor product, then the AE* and/or PQC must be reported according to the AE/PQC reporting table (Table 2). The investigator must evaluate each SAE for causality and record causality on the report form for each SAE and NSAR reported.

*For the purposes of primary data collection, **the term "AE" collectively refers to the following reportable events** (refer to Section 8.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause
- Non-serious adverse reactions (NSARs)
- Special situations

Secondary Chart Review: Although AEs and PQCs are not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs will be reported. For example, during review of medical records or physician notes (paper or electronic) to collect data as required by the protocol, if a notation of an AE* or PQC to RECARBRIO or any other Sponsor product is identified, the AE/PQC must be reported according to the AE/PQC reporting table (Table 2).

*For the purposes of secondary chart review, **the term "AE" collectively refers to the following reportable events** (refer to Section 8.2 for definitions):

- Serious adverse reactions (SARs), including death
- Non-serious adverse reactions (NSARs)
- Special situations

Primary Data Collection and Secondary Data Collection: AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to the AE/PQC reporting table (Table 2).

If any health outcomes are described in Section 6.3.2, they must be assessed for AE reportability according to the AE/PQC reporting table (Table 2).

Table 2 AE and PQC Reporting Timeframes and Process for Investigators

AEs AND PQCs	**INVESTIGATOR TIMEFRAMES Investigator to Sponsor [1,2]**
SAE regardless of causality *(primary data collection)* SAR (secondary chart review) Serious Special Situation, regardless of causality	24 hours from receipt
NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt
PQC with or without an AE (SAE/SAR/NSAR/Special situation)	24 hours from receipt
Follow-up to any AE-submit using above timeframes	
BD-Business Day; CD-Calendar Day	
Non-Sponsor Products: If the investigator elects to submit AEs/PQCs for **non-Sponsor products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.	
[1] Investigator to Sponsor: AEs and PQCs for Sponsor study product and other Sponsor products are submitted to Sponsor for reporting to worldwide regulatory agencies as appropriate [2] Investigator to Study Lead: Study Lead ensures AEs for Sponsor study product are entered into study database (or equivalent repository) for tabulation in study report.	
Submitting AEs and PQCs: All AEs and PQCs must be submitted using AE/PQC reporting form to MSD via https://safetyreporting.msd.com/ (choose Country Submit Report link). If any time the portal is experiencing technical difficulties, information should be sent via Fax 010-58609044.	

8.1.2 Study Report

The final study report, and any planned interim analysis, will include a summary of all reported AEs and special situations collected for RECARBRIO and will be provided to regulatory agencies by the sponsor as required.

8.1.3 Periodic Safety Update Reports

Any relevant safety information will be summarized, and the Sponsor will include in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

8.2 Definitions

8.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

8.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

8.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

8.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in Section 8.2.3.

8.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

8.2.6 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

8.2.7 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

8.2.8 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

8.2.9 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

Secondary Data Collection (Chart Review)

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

8.3 AE Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs will be reconciled on a periodic basis.

8.4 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

9 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The primary results of this research study will be externally disseminated in a manuscript submitted to a peer-reviewed, scientific journal, abstract/presentation at a scientific conference or symposium, or results posted on the HMA-EMA Catalogue of RWD Studies. Prior to external dissemination all sponsor publication requirements must be met, this includes but is not limited to completion of all authorship requirements. Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally. Any publication resulting from this work will adhere to the procedures and pre-specified analysis plans within this protocol.

10 MILESTONES

Milestone	Planned Date
Registration on the HMA-EMA Catalogue of RWD Studies	Q2 2026
Start of data collection	Q4 2026
End of data collection	Q1 2028
Final report of study results	Q4 2028

11 REFERENCES

[1] World Health Organization (WHO). WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva (Switzerland): World Health Organization (WHO); 2024. 70 p. [09534S]

[2] CHINET Data Cloud [Internet]. [place unknown]: China Antimicrobial Surveillance Network (CHINET); [cited 2026 May 27]. Bacterial classification by year statistics; [cited 2026 May 27]; [about 3 screens]. Available from: https://www.chinets.com/Data/GermYear. [09540C]

[3] World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS). Global antibiotic resistance surveillance report 2025: summary. Geneva (Switzerland): World Health Organization (WHO); 2025. 20 p. [09530K]

[4] Bonkat G, Bartoletti R, Bruyere F, Cai T, Geerlings SE, Koves B, et al. EAU guidelines on urological infections. Arnhem (The Netherlands): European Association of Urology; 2024 Apr. 92 p. [0952XS]

[5] Tandogdu Z and Wagenlehner FME. Global epidemiology of urinary tract infections. Curr Opin Infect Dis. 2016 Feb;29(1):73-9. [050HKT]

[6] Ren N, Wen Xm, Wu Ah. [Nationwide cross-sectional survey on healthcare-associated infection in 2014]. Chin J Infect Control. 2016 Feb;15(2):83-7. Chinese. [05Q6X0]

[7] Peng D, Li X, Liu P, Luo M, Chen S, Su K, et al. Epidemiology of pathogens and antimicrobial resistance of catheter-associated urinary tract infections in intensive care units: a systematic review and meta-analysis. Am J Infect Control. 2018;46:e81-90. [080LPK]

[8] Li X, Chen Y, Gao W, Ye H, Shen Z, Wen Z, et al. A 6-year study of complicated urinary tract infections in southern China: prevalence, antibiotic resistance, clinical and economic outcomes. Ther Clin Risk Manag. 2017;13:1479-87. [05Q6VZ]

[9] Feng G, Zhiyong L, Lu K. Expert consensus on the diagnosis and treatment of carbapenem-resistant organisms in complex intra-abdominal infection (2025 edition). Chin J Dig Surg. 2025 Nov;24(11):1397-412. [0952Y7]

[10] Sartelli M, Abu-Zidan FM, Catena F, Griffiths EA, Di Saverio S, Coimbra R, et al. Global validation of the WSES Sepsis Severity Score for patients with complicated intra-abdominal infections: a prospective multicentre study (WISS Study). World J Emerg Surg. 2015;10:61. [095329]

[11] Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990 Nov;132(5):910-25. [04474R]

[12] Moss M. Epidemiology of sepsis: race, sex, and chronic alcohol abuse. Clin Infect Dis 2005;41(Suppl 7):S490-S497. [03RCS4]

[13] Blanco J, Muriel-Bombín A, Sagredo V, Taboada F, Gandía F, Tamayo L, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Crit Care 2008;12(6):R158. [03RCVS]

[14] Zhang J, Zhao C, Chen H, Li H, Wang Q, Wang Z, et al. A multicenter epidemiology study on the risk factors and clinical outcomes of nosocomial intra-abdominal infections in China: results from the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) 2007-2016. Infect Drug Resist. 2018;11:2311-8. [0952WW]

[15] Xi-mao W, Nan R, An-hua W, Xun H, Qiu-ping F, Yun Y, et al. [Prevalence rates of postoperative lower respiratory tract infection of National Healthcare-associated Surveillance Network in 2016]. Chin J Infect Control. 2018 Aug;17(8):653-9. Chinese. [080LPN]

[16] Liu YN, Cao B, Wang H, Chen LA, She DY, Zhao TM, et al. Adult hospital acquired pneumonia: a multicenter study on microbiology and clinical characteristics of patients from 9 Chinese cities. Zhonghua Jie He He Hu Xi Za Zhi. 2012 Oct;35(10):739-46. [04TVX0]

[17] Shi Y, Huang Y, Zhang TT, Cao B, Wang H, Zhuo C, et al. Chinese guidelines for the diagnosis and treatment of hospital-acquired pneumonia and ventilator-associated pneumonia in adults (2018 Edition). J Thorac Dis. 2019 Jun;11(6):2581-616. Supplemental material; 3 p. [05FRRS]

[18] Yin Y, Zhao C, Li H, Jin L, Wang Q, Wang R, et al. Clinical and microbiological characteristics of adults with hospital-acquired pneumonia: a 10-year prospective observational study in China. Eur J Clin Microbiol Infect Dis. In press 2020. [05MJ6S]

[19] Feng DY, Zhou YQ, Zou XL, Zhou M, Yang HL, Chen XX, et al. Elevated blood urea nitrogen-to-serum albumin ratio as a factor that negatively affects the mortality of patients with hospital-acquired pneumonia. Can J Infect Dis Med Microbiol. 2019 Jun 16;2019:1547405. [086XLD]

[20] Huang Y, Jiao Y, Zhang J, Xu J, Cheng Q, Li Y, et al. Microbial etiology and prognostic factors of ventilator-associated pneumonia: a multicenter retrospective study in Shanghai. Clin Infect Dis. 2018;67(suppl 2):S146-52. [086XK6]

[21] Jiao J, Li Z, Wu X, Cao J, Liu G, Liu Y, et al. Risk factors for 3-month mortality in bedridden patients with hospital-acquired pneumonia: a multicentre prospective study. PLoS One. 2021 Mar 30;16(3):e0249198. [086XK7]

[22] Song X, Chen Y, Li X. Differences in incidence and outcome of ventilator-associated pneumonia in surgical and medical ICUs in a tertiary hospital in China. Clin Respir J. 2014;8:262-8. [086XK9]

[23] Zeng M, Xia J, Zong Z, Shi Y, Ni Y, Hu F, et al. Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. Chin J Infect Chemother. 2024 Mar;24(2):135-51. [09532W]

12 ANNEXES

Annex 1 Administrative and Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence. If applicable such information will be divulged to Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and study site personnel (if applicable), may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. By signing this protocol, the investigator expressly consents to these uses and disclosures. Additionally, the investigator's name and business contact information may be included when reporting

certain serious adverse events to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study

for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ECs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, the Sponsor will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to

allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), as well as the European Medicines Agency GVP Module VIII, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to one or more study registries such as the HMA-EMA Catalogue of RWD Studies. The Sponsor of this study will review this protocol and submit the information necessary to fulfill these requirements as appropriate. Information posted will allow subjects to identify potentially appropriate primary data collection studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA and EMA GVP Module VIII are that of the Sponsor and agrees not to submit any information about this study or its results to a study registry without consulting with the Sponsor.

Annex 2 ENCePP Checklist for Study Protocols

Confidential

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Post-marketing study to assess the effectiveness and safety of RECARBRIO in Chinese adult patients with limited or no alternative treatment options for susceptible Gram-negative bacterial infections

EU PAS Register® number:
Study reference number (if applicable): 7655A-035

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Progress report(s)	☐	☒	☐	2
1.1.4 Interim report(s)	☐	☒	☐	2
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4.2
2.1.2 The objective(s) of the study?	☒	☐	☐	5
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	6.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	6.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	6.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	6.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	8

Comments:

Section 4: Source and study populations	***Yes***	***No***	***N/A***	***Section Number***
4.1 Is the source population described?	☒	☐	☐	6.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6.2.4
4.2.2 Age and sex	☒	☐	☐	6.2.1
4.2.3 Country of origin	☒	☐	☐	6.2.1
4.2.4 Disease/indication	☒	☐	☐	6.2.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.5 Duration of follow-up	☒	☐	☐	6.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	6.2.2, 6.5.1

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	6.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	6.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	6.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	6.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	6.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	6.3.3

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	6.11
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	6.11

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	6.9

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	6.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	6.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	6.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	6.4
9.3 *Is a coding system described for:*				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	6.9
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	6.9
9.3.3 Covariates and other characteristics?	☒	☐	☐	6.9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 9.3 and 9.4 will be further detailed in a stand-alone DMP.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	6.9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	6.6
10.3 Are descriptive analyses included?	☒	☐	☐	6.9
10.4 Are stratified analyses included?	☒	☐	☐	6.9
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	6.3, 6.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	6.9

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7
11.2 Are methods of quality assurance described?	☒	☐	☐	6.10
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	6.11
12.1.2 Information bias?	☒	☐	☐	6.11
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.11

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	7
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	7
13.3 Have data protection requirements been described?	☒	☐	☐	7

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:
It is the original version.

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9

Comments:

Name of the main author of the protocol: PPD

Date: 10/April/2026

Signature: _____

Annex 3 Seriousness Assessment of Adverse Events

SAE is any AE occurring at any dose or during any use of Sponsor's product that:

Serious Term	Assessment Criteria
Results in death	
Is life-threatening	or places the patient, in the view of the investigator, at immediate risk of death from the experience as it occurred (Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death); or
Results in hospitalization or prolongs an existing inpatient hospitalization	Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.);
Results in a persistent or significant disability/incapacity	Substantial disruption of one's ability to conduct normal life functions
Is a congenital anomaly/birth defect	In offspring of patient taking the product regardless of time to diagnosis
Is an otherwise important medical event	Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Annex 4 Causality Assessment of Adverse Events

Table 3 WHO-UMC Causality Categories

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge* satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

* Rechallenge: Was the patient re-exposed to the drug during this study? If yes, did the AE recur or worsen upon re-exposure? If yes, this is considered a positive rechallenge; if not, this is considered a negative rechallenge. *Note:* This criterion is not applicable if the initial AE resulted in death or permanent disability, or if the drug is a single-dose product.

13 SIGNATURES

13.1 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.3 Sponsor's Study Lead

PRINTED NAME	PPD
TITLE	Associate Principal Scientist, Epidemiology Asia-Pacific Unit
SIGNATURE	
DATE SIGNED	