STUDY
A retrospective chart review study of cefiderocol real world outcomes and safety in the treatment of patients with Gram-negative bacterial infections (GNBI) in the USA and Europe
PROVE (Retrospective Cefiderocol Chart Review Study)

Non-interventional Study Protocol: 2020-266-1

Version 1.0 EU
23 March 2021

Study Sponsor EU
Shionogi B.V.

This study will be conducted in compliance with the protocol and applicable local regulatory requirements.

CONFIDENTIAL

Approval of Protocol

Study Protocol Title: **A retrospective chart review study of cefiderocol real world outcomes and safety in the treatment of patients with Gram-negative bacterial infections (GNBI) in the USA and Europe**

Study Protocol Number: **2020-266-1**

Version Number: **1.0 EU**

Issue Date: **23 March 2021**

Sponsor Signatory:

This study protocol has been reviewed and approved by:

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31 March 2021

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Investigator

I have read and agree to the protocol 2020-266-1 entitled ‘A retrospective chart review study of cefiderocol real world outcomes and safety in the treatment of patients with Gram-negative bacterial infections (GNBI) in the USA and Europe’. I am aware of my responsibilities as an Investigator under local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Hospital Name and Address:

Hospital Principal Investigator:

Print Name Title

Signature Date

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AWS	Amazon Web Services
CDC	U.S. Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CR	Carbapenem Resistant
CRO	Clinical Research Organization
EC	Ethics Committee
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU-5	France, Germany, Italy, Spain, and UK
FDA	U.S. Food & Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GN	Gram-negative
GNBI	Gram-negative Bacterial Infection
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HIPPA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
ID	Identification
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LOS	Length of Stay
PI	Principal Investigator
PV	Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
WHO	World Health Organization

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3 ABSTRACT/SYNOPSIS

Name of Sponsor: Shionogi

Title of Study: A retrospective chart review study of cefiderocol real world outcomes and safety in the treatment of patients with Gram-negative bacterial infections (GNBI) in the USA and Europe.

Study Centers: The study will target approximately 1000 patients meeting the selection criteria from approximately 100 sites: 50% of patients from the USA, 50% of patients from 5 European countries: France, Germany, Italy, Spain, and the UK. Each study site can include up to 20 patients.

Planned Study Dates: Data collection will take place between 1 December 2020 – 31 December 2022. Data will be entered on the study database over an estimated 2 months in approximate 6-month intervals.

Objectives: The study intends to understand the clinical characteristics, cefiderocol use, other antibiotics use, microbiology, outcomes and safety of patients treated with cefiderocol for **the indicated GNBI (**defined as the documented GNBI that prompted the cefiderocol use).

Primary Objective:

- To describe the clinical characteristics (comorbidity, underlying disease, admission diagnosis), microbiological characteristics (pathogens, susceptibility results, including MIC to cefiderocol), outcomes and safety of patients treated with cefiderocol.

Secondary Objectives:

- To describe how cefiderocol is used, including infection sites and dosing regimen
- To describe the overall in-hospital mortality of patients and by specific pathogen
- To describe clinical outcomes of the indicated GNBI after cefiderocol treatment
- To describe the number and type of adverse events related to cefiderocol
- To describe the patient population characteristics treated with cefiderocol

Study Design and Methodology: This is a multi-site, retrospective chart review of existing medical records in patients prescribed cefiderocol for the first time.

At each site, a specific chart reviewer with access to patient records will identify sequential patients who received their first cefiderocol treatment for a Gram-negative bacterial infection (GNBI) during hospitalization. At each 6-month study interval in a 2-month data collection 'wave', following assessment of the patient's eligibility for the study, the reviewer will extract the following data for each eligible patient: demographics, clinical characteristics, microbiological results, antibiotic susceptibility, antibiotic usage, clinical outcome of the indicated GNBI and in-hospital mortality or discharge status from the medical charts. The reviewer will enter the extracted data, excluding any patient identifiers, into a secure, password-protected online portal. The principal study investigator will review the data and make the final submission to the online portal.
Since this is a retrospective chart review study, the study does not influence antibiotic usage, study visits, tests, sampling or procedures and does not pose any risk for patients.

The study will obtain written patient consent for study participation and sharing their data across the regions according to the regulations and practice in each country or region before data collection. Where assumed consent is permissible in the absence of formal written consent, this will be utilized in accordance with local regulations. If the patient has died before data collection, a legally acceptable representative (such as a family member or relative) will be contacted for consent if required by local regulations.

Study Population and Inclusion/Exclusion Criteria: Each study site will include up to 20 patients in total during the data collection waves who meet the inclusion criteria and do not meet the exclusion criteria. If a site has more than 20 patients, the most recent 20 patients will be selected.

Inclusion criteria:

- All patients with a documented GNBI (before or after starting cefiderocol) who had received continuous cefiderocol treatment for at least 72 hours as a routine practice for the first time
- Patients with the following documented essential data elements:
    - Start and stop dates of cefiderocol and dosing regimen (dose, duration, frequency)
    - Documentation of a GNBI (infection site, pathogen) that can be directly linked to use of cefiderocol
    - The outcome information of the indicated GNBI at the end of the cefiderocol treatment
    - The outcome of the hospitalization: in-hospital mortality or discharge status
- Documented evidence of informed consent by the patient (or a legally acceptable representative) where required by local or country regulations.

Exclusion criteria:

1. Patients with incomplete medical records for essential data elements on cefiderocol use, infection and outcome assessment.
2. Patients receiving cefiderocol through a clinical trial, compassionate use, early access program, or other means before cefiderocol is commercially available in the respective country.
3. Patients having prior treatment with cefiderocol before the current hospitalization.

Number of Patients: Since this is a descriptive study to estimate the rate of success and safety event, not a hypothesis-testing one, there is no sample size calculation. However, the study will collect information on approximately 1000 patients during the study period from the US (500 patients), France (100 patients), Germany (100 patients), Italy (100 patients), Spain (100 patients), and the United Kingdom (100 patients). This sample size will give us a 95% confidence that the true event rate (e.g., binary endpoint such as mortality) is $\leq 0.3\%$ even if the event is not observed in the study. The study will monitor the pace of patient data collection to ensure that all countries can contribute patients to the study.

Study Treatment(s): Cefiderocol

Study Evaluations: The plan for evaluation is to have the first interim analysis in April 2021. The final study report will be issued in June 2023. Key study variables and the outcomes are below.

Key study variables: (detail in section 8.4.3)

- Demographic data
- Comorbid conditions and risk factors for CR infection
- Clinical and microbiological detail of the indicated GNBI
- Cefiderocol use data including rationale for usage dosage, duration of treatment and adverse drug reactions.
- Concomitant or prior usage of other antibiotics

Key study endpoints:

The following endpoints will be prescribed for the study as a whole and by CR status or infection sites:

- Description of patient characteristics
- Description of type of infection and GN pathogen (pathogen name, infection site, mono-bacterial infection vs. mixed bacterial infections, source of infections)
- Usage of cefiderocol (empirical vs. definitive use, duration, monotherapy or in combination with other antibiotics)
- Clinical resolution of the indicated GNBI at the end of cefiderocol treatment (% of patients and time to resolution - median)
- Microbiological cure of GN pathogen for the indicated GNBI at the end of cefiderocol (% of patients and median time to microbiological cure among those with repeated microbiologic results)
- In-hospital all-cause mortality
- Duration of hospitalization in days (total and post-infection)
- Length of ICU stay during hospital admission (total and infection associated)
- Number and type of adverse drug reactions associated with cefiderocol

A statistical analysis plan (SAP) will be prepared separately to document the data handling, derivation of the study endpoints and different types of analyses, including subgroup analyses.

Statistical Methods: Descriptive statistics will be used to describe all collected data. The study will use mean, standard deviation, median and interquartile range to describe the continuous variables. It will use frequency, percentage and corresponding 95% confidence intervals to describe the categorical variables. Risk factors for infection will be assessed using univariable and multivariable logistic regression. Predictors of outcomes such as mortality and LOS will also be explored with logistic and linear multiple regression where appropriate.

4 STUDY MILESTONES

Complete study synopsis and draft eCRF/ questionnaire	May 2020
Final study protocol version 1.0	October 2020
US Field testing study eCRF/questionnaire	November 2020
US Final study questionnaire	February 2021
Online portal ready for data entry	March 2021
First US site completes IRB and contract	March 2021
Wave 1 of data collection – US only	March-April 2021
First patient data entered	March 2021
EU amends to protocol and questionnaire	February 2021
EU protocol version 1.0	March 2021
First interim report/abstract	April 2021
First EU site completes EC approval and contract	May 2021
First EU patient data entered	June 2021
Wave 2 of data collection – US + EU countries*	June-July 2021
Wave 3 of data collection – US + EU countries*	November-December 2021
Wave 4 of data collection – US + EU countries*	June-July 2022
Wave 5 of data collection – US + EU countries*	November-December 2022
Last patient data entered	December 2022
Site close-down initiated	December 2022
Final study analyses completed	March 2023
Final study report	June 2023

* Where cefiderocol has been launched commercially and data are available

5 BACKGROUND AND STUDY RATIONALE

Treatment of infections of Gram-negative pathogens is complicated by the rise and spread of antibiotic-resistant strains such as carbapenem-resistant (CR) Enterobacteriaceae species, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. WHO and CDC consider the carbapenem resistance in *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* as an urgent threat to global public health [WHO, 2017; CDC, 2019]. Any delay in management, or inadequate antibiotic therapy of Gram-negative bacterial (GNBI), can have serious consequences for prognosis [Bonine et al., 2018].

Cefiderocol is a first in class, injectable siderophore cephalosporin that combines a "catechol-type siderophore and cephalosporin core with side chains similar to cefepime and ceftazidime" [Wu et al., 2019]. In addition to entering cells by passive diffusion through porin channels, cefiderocol binds to ferric iron and is actively transported into bacterial cells through the outer membrane via the bacterial iron transporters, which function to incorporate this essential nutrient for bacteria [US package insert, 2019]. These mechanisms allow cefiderocol to achieve high concentrations in the periplasmic space where it can bind to penicillin-binding proteins and inhibit cell wall synthesis in the bacterial cells. Cefiderocol's "structure" and its unique mechanism of action confer enhanced stability against hydrolysis by many β-lactamases, including extended spectrum β-lactamases such as CTX-M, and carbapenemases such as KPC, NDM, VIM, IMP, OXA-23, OXA-48-like, OXA-51-like and OXA-58 [Wu et al., 2019].

Cefiderocol received US Food and Drug Administration approval on 14th November 2019 for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex in patients 18 years of age or older who have limited or no alternative treatment options [US package insert, 2019] and on 25th September 2020 for nosocomial pneumonia (HABP/VABP) and infections caused by carbapenem-resistant Gram-negative pathogens [US package insert, 2020].

Cefiderocol also received European Medical Agency approval in 29th April 2020 for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options [EMA, 2020]

Given the strict inclusion and exclusion criteria and limited number of patients included in the pivotal phase 3 studies, additional evidence on the efficacy and safety evidence of cefiderocol in real-world use is of value to supplement existing data. Shionogi has developed this global observational research study via a retrospective chart review to fill this gap. This chart review will collect patient data on clinical and demographic characteristics, utilization of cefiderocol and other antibiotics, microbiology, and outcomes of patients treated with cefiderocol for documented GNBI that prompted or was associated with the use of cefiderocol.

6 STUDY OBJECTIVES

6.1 Primary Objective

- To describe the clinical characteristics (comorbidity, underlying disease, admission diagnosis), microbiological characteristics (pathogens, susceptibility results including MIC to cefiderocol) outcomes and safety of patients treated with cefiderocol.

6.2 Secondary Objectives

- To describe how cefiderocol was used, including infection sites and dosing regimen
- To describe the patient population characteristics treated with cefiderocol
- To describe the overall in-hospital mortality of patients and by specific pathogen
- To describe the clinical outcome of the indicated GNBI after cefiderocol treatment
- To describe the number and type of adverse events related to cefiderocol treatment

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a multi-site, retrospective chart review of existing medical records in patients treated with cefiderocol for the first time. It is designed and will be conducted according to the requirements of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [ENCePP, 2015] and International Society for Pharmacoepidemiology (ISPE) guidance [ISPE, 2015] and ICH GCP as appropriate.

At each site, a chart reviewer employed by the study site with access to patient medical records will be identified. Before each 2-month data collection wave in every 6-month study cycle, the reviewer will identify all the patients who received their first course of cefiderocol treatment for a Gram-negative bacterial infection (GNBI) during hospitalization in the previous 6 months. These patients will either have been discharged alive from the hospital or died in the hospital. The documented GNBI that prompted cefiderocol use is defined as the **indicated GNBI**. After assessing a patient's eligibility for the study, the reviewer will extract the following data for each eligible patient; demographics, clinical characteristics, microbiological results, antibiotic susceptibility, antibiotic usage, clinical outcome of the indicated GNBI and in-hospital mortality or discharge status from the medical charts. The time interval for data extraction for each patient will start with the admission date and end with the discharge date from the same episode of hospitalization or the date of death if occurring in the same hospital stay. Data will be collected only once for each patient. Data will be collected sequentially with the most recent patient included first. A full list of variables can be found in section 6.4.3 of this protocol.

Since this is a retrospective chart review study, the decision to treat patients with cefiderocol will have been made already by the treating physicians within their practices; this protocol has no influence on that decision. This protocol does not influence antibiotic usage, study visits, tests, sampling or procedures and does not pose any risk for patients.

7.2 Study Duration, Enrolment and Number of Sites:

Data collection is planned for a total of 24 months between December 2020 to December 2022. Cefiderocol must be available commercially for at least 6 months in each country before data collection in that country can begin.

Study sites will be selected based on prior experience of using cefiderocol, availability of medical records for the study, experience in data collection studies and prevalence of resistant GNBI. It is estimated that 50 sites in the US and 10 sites in each of 5 European countries (France, Germany, Italy, Spain, UK) will be included in the study.

Each study site is expected to collect data for 5 to 20 patients who meet the inclusion criteria and do not meet the exclusion criteria. The patients included must have been treated with cefiderocol within 6 months of the commencement of the current data collection wave with the exception of the first wave which may extend further back to onset of commercial availability. If a site has more than 20 eligible patients, the most recent 20 patients will be selected.

7.3 Study Population

All patients treated with cefiderocol according to the site's standard clinical practice during the study period who meet the inclusion criteria and do not meet the exclusion criteria are eligible for inclusion into the study. The study site will select patients starting with the most recent and include the preceding patients in chronological order who satisfy the study criteria up to a maximum of 20 across all data collection waves.

7.3.1 Inclusion Criteria

- All patients with a documented GNBI (before or after starting cefiderocol) who for this infection received continuous cefiderocol treatment for at least 72 hours as routine practice.
- Patients whose medical records include the following essential data elements:
    - Start and stop dates of cefiderocol and dosing regimen (dose, duration, frequency)
    - Documentation of GNBI (infection site, pathogen).
    - The clinical outcome of the indicated GNBI at the end of the cefiderocol treatment
    - The outcome of the hospitalization: in-hospital mortality or discharge status
- Documented evidence of informed consent by the patient (or a legally acceptable representative) where required by local or country regulations.

7.3.2 Exclusion Criteria

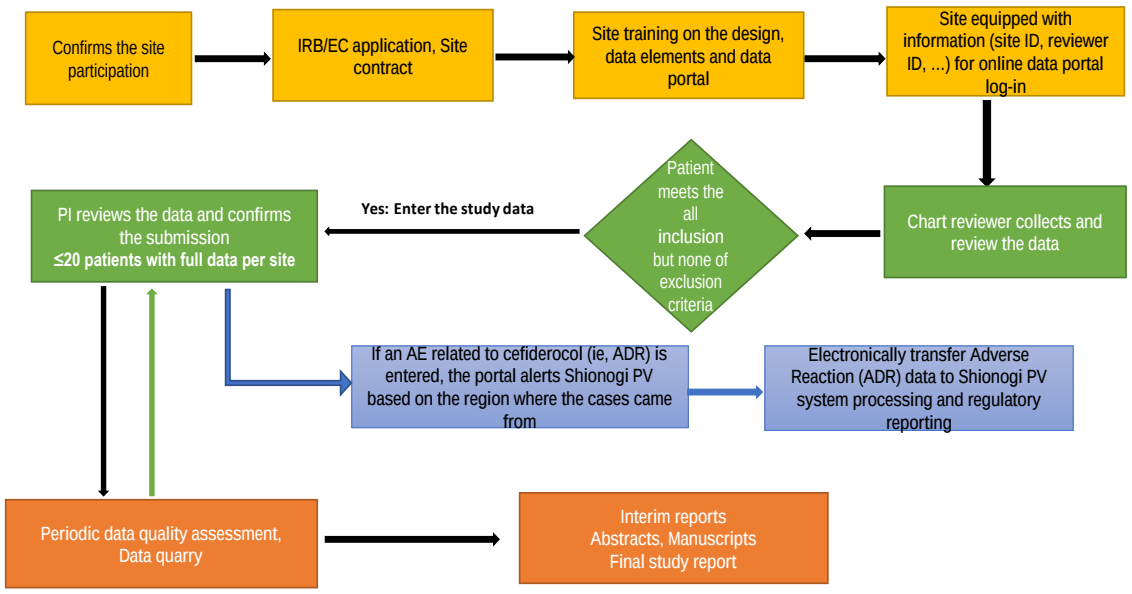
1. Patients with incomplete medical records for essential data elements on cefiderocol use, infection, or outcome assessment
2. Patients receiving cefiderocol through a clinical trial, compassionate use, or early access program, or other means before the cefiderocol is commercially available in the respective country
3. Patients with any prior treatment of cefiderocol before the current hospitalization
4. Patients <18 years old

7.4 Study Procedures

Site staff at each contracted hospital will be required to perform the following tasks upon site initiation and periodically afterwards until final data extraction:

1. Identify all cefiderocol-treated patients within the study timeframe.
2. Provide informed consent forms or notification (when applicable) to all identified cefiderocol-treated patients or a legally acceptable representative (such as a family member or relative) with complete medical records and obtain informed consent, in accordance with, local and country regulations and guidelines.
3. (For sites requiring informed consent only). Keep records of patients sent informed consent forms and number of times followed up, if necessary. All signed consent forms returned should be stored securely with the study documentation in the study site file provided, with restricted access. A record of those patients providing and not providing consent should be stored with the study documentation. Data from patients not providing consent or otherwise notifying the site that he/she does not wish to participate, will not be collected unless this is allowed according to local and country regulations and guidelines.
4. Keep an audit trail of patients included in the study by a unique identification number allocated to them which corresponds to pseudonymized ID and data provided by the CRO in the database.
5. Keep study patient personal information in a secure area with restricted access and ensure that medical records cannot be transferred outside the study site.
6. Complete electronic study eCRF/questionnaire on the data platform for all included patients as defined above.
7. Study principal investigator will review and approve the completed electronic study questionnaire before submitting the data to the study database within the data platform.
8. Respond to all queries from the CRO or Shionogi regarding information recorded in eCRF/questionnaire in a timely manner.

Figure 1. Study Schematic



7.4.1 Data Source

Data will be collected from inpatient medical records and laboratory reports documenting the patient's hospitalization. The study will not collect any additional follow up patient data following discharge from hospital.

7.4.2 Patient Selection

Following initiation, each site will identify all patients treated with cefiderocol in the past 6 months. Data for all eligible patients according to the inclusion and exclusion criteria will be entered on the study database via the designated online data portal in the appropriate data collection wave.

Sites initiated in each country will have the opportunity to participate in as many data collection waves as they wish until the end of the study in order to include up to 20 patients.

For each wave of data collection each participating site will interrogate their database for the period six months prior to the first day of the data collection wave in order to identify new patients treated with cefiderocol and review the medical records up until a cumulative maximum of 20 eligible patients is reached for all waves up to that point. If there are more than 20 patients on the first data review, the PI will include the most recent 20 patients sequentially.

7.4.3 Data Elements to Be Abstracted

The following data will be collected via the study eCRF/questionnaire predominantly by ticking pre-populated boxes. Free text entry is provided where pre-populated answers are not applicable.

- **Patient Demographic data:**
  - Age in years at time of admission
  - Gender
  - Place of patient residence prior to hospital admission
- **Patient Admission Data:**
  - Admission date
  - Admission type
  - Admission diagnosis
  - Relevant pre-existing medical conditions at the time of admission
  - Risk factors for CR-GNBI
- **Infection Course and Microbiology:**
  - Date of onset of the first clinical sign and symptom of the indicated GNBI
  - Primary infection site
  - Signs resulting in index infection diagnosis at the primary and other infection site
  - Pathogen identified as the GNBI
  - Was there source control (removal of presumed infected catheter, prosthesis, fluid collection, etc.?
  - If infection was respiratory, was it ventilator-associated
  - If infection was bacteremia, was it venous-line related
  - Date, time of index culture
  - Patient location when the index culture was obtained
  - Other pathogens identified from the same culture
  - Antibiotic susceptibility testing date
  - Antibiotic susceptibility testing results
  - Carbapenem resistance testing
  - Previous pathogen isolated in patient prior to current hospitalization
- **Antibiotic Use:**
  - Reason for cefiderocol initiation
  - Type of Clinician recommending cefiderocol initiation
  - Cefiderocol start date
  - Cefiderocol dose, infusion time, and frequency
  - Patient body weight
  - Serum creatinine
  - Cefiderocol end date
  - Reason for discontinuation of cefiderocol
  - Other antimicrobials or antifungals started within 14 days prior to commencing cefiderocol or starting 3 days from stopping cefiderocol
  - Assessment of overall clinical benefit of cefiderocol treatment on indicated GNBI
  - Repetition of microbiological samples on cefiderocol discontinuation and result if performed
  - Nature, severity, duration and date of onset of adverse drug reactions related to cefiderocol documented by treating clinicians up to point of hospital discharge
  - Outcome of any adverse drug reaction
  - Action taken if any with regards to cefiderocol due to adverse drug reaction
  - If patient had ICU stay while on cefiderocol during hospitalization, if yes, reason for admission, length of stay, apache 2 score on admission and outcome of ICU stay

- Presence and type of organ support received in ICU.

- **Outcome of Hospitalization:**
  - Date of discharge
  - Discharge status (alive or deceased)
  - If discharged alive discharge location
  - If discharged alive, discharge on IV antibiotics for GNBI
  - If died during current hospitalization, what was the cause of death

8 STATISTICAL ANALYSIS

8.1 Outcome Measurement:

The following endpoints will be examined for all subjects and then stratified by CR status:

8.1.1 Primary Study Endpoints

- Description of patient characteristics
- Description of type of infection (infection site, mono-bacterial infection vs. mixed bacterial infections, source of infections)
- Description of the GN pathogen linked to the use of cefiderocol (pathogen name, susceptibility results including MIC to cefiderocol, multi-drug resistant status)
- Usage of cefiderocol: time from when culture was obtained until first dose, dosage, duration, and whether given as mono therapy or in combination with other antibiotics)
- Clinical resolution of the signs and symptoms of the indicated GNBI at the end of cefiderocol (time to resolution)
- In hospital all-cause mortality
- Duration of hospitalization in days (total, and post-infection)
- Length of ICU stay during hospital admission (total, and infection associated)
- Number and type of adverse drug reactions associated with cefiderocol

8.1.2 Secondary Study Endpoints

- Sub-group analysis of study endpoints stratified by pathogens, infection sites, age groups
- Potential risk factors of CR-GNBI
- Time to clinical cure
- Mortality rate
- Pattern of antibiotic treatments used
- Hospital resource use as measured by post-infection length of stay; ICU length of stay associated with CR-GNBI vs. non-CR-GNBI

8.2 Statistical Methods

Data will be analyzed using the methods described below. A full statistical analysis plan (SAP) will be prepared separately to document the data handling, derivation of the study endpoints, and different types of analyses, including subgroup analyses.

Most analyses will be descriptive in nature. Numbers and percentages with calculated 95% confidence intervals will be used to describe categorical variables. The mean, standard deviation, interquartile, and range will be calculated to describe normally or near-normally distributed

continuous variables. Median and inter-quartile ranges will be used to describe skewed continuous variables. Normality of variables will be conducted through inspection of histograms. Statistics will be presented and stratified by pathogen and pathogen-infection site.

The factors that may influence the study endpoints (efficacy and safety) will be assessed using univariate analyses. Factors determined to be suggestive of an association (p-value < 0.2) of study endpoints from univariate analyses will be selected in a multivariable logistic regression analysis model alongside key patient and disease characteristics.

8.3 Sample Size and Power

Since this is a descriptive study to estimate the rate of success and safety event, not a hypothesis-testing one, there is no sample size calculation. However, the study will collect information on approximately 1000 patients during the study period, half from the US and half from France, Spain, Italy, Germany and the UK. This sample size will give us a 95% confidence that the true event rate (e.g., binary endpoint such as mortality) is ≤ 0.3% even if the event is not observed in the study. The enrolment pace in each country will be monitored to ensure that all countries can contribute patients to the study.

9 STUDY ADMINISTRATION

9.1 Study Management

There are two Clinical Research Organizations involved in the study, hereafter called the EU CRO and the US CRO.

The US CRO selected for this study is responsible for all data management which includes creating and maintaining the data portal and analyzing data from the fully anonymized aggregate database containing information from questionnaires from both Europe and the US. The US CRO will provide training and logistical support for the US sites on behalf of Shionogi in the US. The US CRO will also train the EU CRO on the completion of the data portal so they can train the EU sites.

The EU CRO and Shionogi in Europe will be responsible for the EU operations and managing data collection in the EU.

Successful completion of data entry tasks by all contracted sites will be monitored by the US CRO throughout the study.

Questions on the questionnaire or interpretation of responses to the questionnaire will be directed to specified Shionogi personnel involved with the study, either by the site PI or the responsible CRO.

9.2 Data Collection

Data management will be governed by Standard Contractual Clauses between Shionogi and the US CRO. Details can be found in the Data Management Plan.

One electronic study questionnaire will be completed for each eligible patient included at participating sites. If the patient is treated with cefiderocol again during a new hospitalisation their data cannot be collected again. The questionnaire contains predominantly closed questions

to collect data as described. This form and its contents will be the sole property of Shionogi and should not be made available in any form to third parties, except for authorized representatives of Shionogi, the CROs or appropriate regulatory authorities. Where paper copies of the eCRF/Questionnaire are printed out either in English or translated to a local language, these will need to be kept and stored as source data in the site file provided.

After the chart reviewer enters the study data, the principal study investigator at the site will review the data, approve, and confirm the submission to the data portal.

The online data entry portal will present the user with a sequence of screens that covers sets of questions in the questionnaire. Each question will guide the user through the process of filling out the relevant fields based on the content of answers provided. This will capture only the relevant information and minimize the user's time-requirements.

The portal is broadly accessible via a secure web portal on a variety of electronic devices (e.g. desktop computer, laptop, tablet). It provides three modes of interactive screens to the study site; the login screens that verify data access credentials, data entry screens that provide data entry to the database and data review screens which present the entered data for review before submission to the main database.

At the end of each six-month period, the study portal will be available for a period of 2 months to allow for data entry, so the data collection is conducted in waves. There will be 5 data collection waves throughout the course of the study. During each wave of the data collection, the site will identify retrospectively all new, eligible patients in the previous 6 months whose data has not been extracted before (with the exception of the first wave). The most recently treated patients will be identified for data extraction if the site has more eligible patients than the allotted maximum number. For countries with cefiderocol commercial launch dates towards the end of the study period, data extractions will start in one of the later planned data collection waves.

All participating sites will only have access to view and enter the data for their own patients.

9.3 Data Quality

The online data portal will incorporate a data validation process to minimize data entry errors and ensure data quality. All entered data will be checked for participant eligibility, anomalous responses and completeness by the study data manager (US CRO) using programmed validation checks, in accordance with the data management plan. Data queries will be raised where necessary and site personnel can either confirm the data is correct or make revisions to the data on the portal. At no time will the data manager influence or suggest a response other than to query and verify a response by the site.

Documentation detailing any corrections will be maintained in the data portal audit trail. The collected data will be routinely backed up by the data management system.

Monitoring visits will be arranged at a small number of sites in Europe according to a monitoring plan. A percentage of source data will be checked against the data entered on the portal.

9.4 Data Security & Storage

The online data entry portal will be hosted on two dedicated secure Amazon Web Service (AWS) servers located in data-appropriate regions. All legal framework directed by regions and different national implementations (e.g. Health Insurance Portability and Accountability Act of 1996 (HIPAA) in US and Regulation 2016/679 of the European Parliament and the Council of 27 April 2016 (General Data Protection Regulations - GDPR) in the EU will be followed.

Access controls to the study portal will be established by the US CRO before it becomes accessible (including user identification and authentication, as well as granting and revoking access privileges) and after data access (logging procedures will keep track of every single access, even if it is only an attempt, in a safely kept electronic log; logs will be periodically examined and any irregular events will be further investigated). All logs will be available to the US CRO for review as needed. The data reviewer and the principal investigator will have their own unique ID numbers.

The US CRO will also have access to the data contained within the online data entry portal for the purpose of data validation. The data entered into the online data entry portal is pseudonymized data with an identification key that is comprised of a site ID number, as generated by the US CRO and a sequential patient ID number as entered by each study site. The patient ID number is assigned by the individual site.

Once the PI has approved the patient's chart information and data validation has been completed (see 9.2), including the resolution of any reported ADRs, the data will undergo encryption and become incorporated into the fully anonymized dataset on the same local AWS server. This will occur on a patient by patient basis. Fully anonymized data cannot be linked to the original patient nor the site and will no longer be accessible or identifiable to the chart reviewer or the investigator. At the end of the study, all the pseudonymized data within each site's account on the online portal will be destroyed.

9.4.1 Data Transfers

The fully anonymized data will be transferred electronically from each regional AWS server to Shionogi's secure server in the US using a secure file transfer protocol. This fully anonymized, pooled data will be the basis for creating the analytic datasets to be used by Shionogi and the US CRO for review and analysis.

9.5 Record Retention

The paper Study Site File containing required study documentation will be archived according Shionogi's record retention policy for at least 5 years after the study termination or other period according to applicable local country requirement(s), whichever is later. All paper files will be securely destroyed at the end of the specified archive period on the instruction of Shionogi, according to Shionogi procedures as appropriate.

9.6 Strengths and Limitations

9.6.1 Strengths

This observational study will add to the body of knowledge on cefiderocol use in the real-world setting in the US and the EU. It will also provide desired information on the safety among patients treated with cefiderocol at approved doses over time in a real-world setting.

Collecting data at the site level allows linkage among inpatient diagnosis, medication, and microbiology data (where available); such linkage is not accommodated by currently available secondary healthcare databases in these countries.

9.6.2 Limitations

Case classification may be affected by the availability of information for microbiological and clinical assessments.

If patient use of cefiderocol is low in some of the participating countries, this study will have a relatively small sample size for those countries.

The study will not collect data outside the patients' hospitalization when they were included in the study. Therefore, it will not contain long-term follow-up data.

10 ETHICAL CONSIDERATIONS

10.1 Risk and Benefit of the Study

Where hard copy patient medical records are accessed by the site in order to input information into the online study portal, there is a risk of a data security breach by the hospital site staff. At site initiation, the site will be asked to confirm that they have adequate procedures in place to safeguard patient medical records accessed for the purpose of the study.

As pseudonymous data will be held within a cloud-based server, an IT security breach is also a risk associated with this study. However, technical and organizational measures have been put in place to mitigate this risk.

The patients whose records will be reviewed are unlikely to receive any benefit from this study but the public may benefit from the knowledge gained from the study.

10.2 Patient Information and Consent (where applicable)

All parties will ensure the protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by local laws.

This is a non-interventional, retrospective medical records review study. All relevant local and country regulations and guidelines will be followed pertaining to informed patient consent. Where assumed consent is permissible in the absence of formal written consent, this will be utilized in accordance with local regulations. If the patient has died before data collection, a legally acceptable representative (such as a family member or relative) will be contacted for

consent if required by local regulations. These local and country specific considerations will be set out in the Study Regulatory Plan before the study starts and before the first patient consent.

The informed consent forms (where required according to local laws) must be compliant with local and country regulatory and legal requirements. The informed consent forms used in this study and any changes made during the study, must be approved by the relevant IRB or EC before use. Study subjects can change their mind about inclusion in the study provided that the notification of change of mind is received prior to the anonymization process set out in Section 8.2. After that point it will not be possible to retrieve or remove their data.

10.3 Ethics Approval

Where required by local laws and regulations ethical approval will be sought from all institutions taking part in the study before any study related activities can begin. Submission of documentation for approval will be conducted according to local and country regulatory requirements and the required critical documents filed accordingly. Local and country requirements will be documented in the Regulatory Study Plan.

Any action resulting in a temporary or permanent suspension of the study will be reported to the appropriate IRB or EC and competent authority if required.

10.4 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by ISPE [ISPE, 2015], International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS) [CIOMS, 2009], European Medicines Agency (EMA) ENCePP Guide on Methodological Standards in Pharmacoepidemiology [ENCePP, 2020], and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, Guidance for Industry [FDA, 2005] and ICH GCP E6 and the Declaration of Helsinki.

10.5 Compensation

As this is a non-interventional study, no compensation will be provided to patients.
Study sites, site staff and principal investigators will be compensated for time spent in completing study requirements consistent with local prevailing conditions. This compensation schedule will be determined in accordance with national and local IRB or EC guidelines and fair market value for the work performed.

10.6 Funding Sources

Shionogi is the study sponsor.

10.7 Conflict of Interest

Some of the study investigators may have been paid consultants to Shionogi before or during this study, including those on the Steering Committee. The investigators in question have been consulted solely to ensure scientific rigour and accuracy of the study as pertains to achieving its objectives.

11 SAFETY MANAGEMENT

Since the study is concerned with secondary data collection, regulatory-required reporting of adverse events and reactions (related adverse events), including of lack of efficacy, medication errors, and off label use, may not be required according to GVP Module VI [EMA, 2016]. However, irrespective of regulatory-mandated reporting, the study will collect adverse events (AEs) that have been clearly documented to be associated with cefiderocol (and can therefore be considered adverse drug reactions, ADRs) and conduct interim safety analysis summaries and the final study report. Reporting of ADRs is described below.

11.1 Study Reportable Events

An adverse event (AE) is any untoward medical occurrence in a patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product (see GVP Annex IV, ICH-E2D Guideline) [EMA, 2004].

A serious adverse event (SAE) is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death.
- A life-threatening adverse experience.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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 outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Since this study retrospectively reviews the patient medical chart, the chart reviewer may not have enough information to assess the causal relationship of AE to the study drug. This study will only collect AEs or SAEs which have been documented in the medical chart to be explicitly associated with cefiderocol and can therefore be considered an Adverse Drug Reaction (ADR). The study will collect the description of the event, onset date and time, severity, and outcome, according to Shionogi's Pharmacovigilance policy.

The reporting period for adverse events will last until the end of the retrospective medical chart review period for each patient (i.e., end of the patient's hospitalization).

11.2 Pharmacovigilance Reporting

When an ADR is entered in the database, the system will automatically send an email alert to the Shionogi Pharmacovigilance (PV) Department in the US (Product Safety and

Pharmacovigilance) or Europe (SEU Safety) based on the country where the case originated. The regional PV department will receive the electronic adverse drug reaction data from the study database, enter it into the Global Safety Database, then process regulatory submission, if applicable, according to local regulatory guidance and Shionogi's internal processes.

12 PUBLICATION AND CONFERENCE PRESENTATIONS

The findings from this study will be shared with the public through presentation in an annual professional conference and/or in a peer-reviewed journal. Any publication plan will be agreed by and in concert with all the investigators with the authorship determined following the guidelines of the International Committee of Medical Journal Editors (ICMJE).

13 REFERENCES

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14 APPENDIX

Protocol History:

Protocol Name	Date	Rationale
Master Protocol V1.0	16 October 2020	Original
V1.0 EU Protocol	23 March 2021	Protocol based on master protocol incorporating local requirements specific to the conduct of the study in Europe