SHIONOGI

SHIONOGI & CO., LTD.
1-8, Doshomachi 3-chome, Chuo-ku
Osaka 541-0045, Japan
Tel: +81-6-6202-2161

Essential Medicines List Secretariat
Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27, Switzerland

November 30, 2020

Dear Essential Medicines Committee:

Shionogi & Co., Ltd. submits this application to request the inclusion of cefiderocol (FETCROJA/ FETROJA) on the World Health Organization (WHO) Model List of Essential Medicines (EML).

Cefiderocol is a novel siderophore cephalosporin antibiotic discovered and developed by Shionogi. Cefiderocol has a unique mechanism of entry, binding to extracellular free iron and entering the periplasmic space through siderophore uptake systems. A broad range of Gram-negative bacteria are susceptible to cefiderocol, including WHO priority pathogens carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, and extended-spectrum β-lactamase-producing Enterobactericeae. Cefiderocol is indicated for treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options in the EU.

We are recommending cefiderocol for inclusion on the EML because antimicrobial resistance is a growing, world-wide problem, and access to effective treatment options can reduce the mortality from these infections. Several multi-national in vitro and clinical studies have demonstrated that cefiderocol offers coverage of multidrug resistance pathogens when there are limited – or no – treatment options available, while keeping a safety profile that is consistent with other cephalosporins.

In 2019, the EML Antibiotics Working Group adopted the Access, Watch, Reserve (AWaRe) classification for antibiotics, tiering antibiotics based on their spectrum of activity and potential for resistance development. Based on these classifications, we recommend inclusion of cefiderocol as a Reserve Group antibiotic, which includes antibiotics that should be reserved for treatment of confirmed or suspected infections due to multidrug-resistant organisms. With Reserve classification, access to cefiderocol should be balanced with appropriate use and strong stewardship.

We strongly recommend the inclusion of cefiderocol on the EML for adults and appreciate your consideration of our application.

Sincerely,

Signature here

Takuko Sawada
Director and Executive Vice President and
Senior Vice President of Integrated Disease Care Department

Application for inclusion of FETCROJA/FETROJA (cefiderocol) on the WHO Model List of Essential Medicines

Submitted to:
WHO Essential Medicines List Secretariat
Expert Committee on the Selection and Use of Essential Medicines
Essential Medicines Team
Medicines Selection, IP and Affordability (MIA)
Department of Health Products Policy and Standards (HPS)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland
Email: emlsecretariat@who.int

Applicant:
Shionogi & Co., Ltd.
1-8, Doshomachi 3-chome, Chuo-ku,
Osaka 541-0045, Japan
Tel : +81-6-6202-2161

Point of Contact:
Monika Schneider
Director, Global AMR Policy
Email: monika.schneider@shionogi.com
Tel: +1-973-936-3275

Date of Submission: November 30, 2020

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1. Summary statement of the proposal for inclusion, change or deletion

Cefiderocol is being proposed for inclusion in the WHO Model List of Essential Medicines under the Reserve Group Antibiotics, which includes antibiotics reserved for the treatment of confirmed or suspected infections due to multi-drug-resistant organisms.

Cefiderocol is a parenteral siderophore cephalosporin antibiotic discovered and developed by Shionogi. The main feature of cefiderocol is its potent activity against a broad spectrum of Gram-negative pathogens, including WHO Priority Pathogens carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobactericeae (1).

Cefiderocol has received FDA approval for complicated urinary tract infection (cUTI) and hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) indications, and EMA approval for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. This latter indication is pathogen focused and supports use in hospitalized patients with a confirmed or suspected carbapenem-resistant infection and where cefiderocol is the best option based on pathogen susceptibility information and/or where other treatment choices are inappropriate. Pathogen-focused prescribing aligns with appropriate use related to diagnostic testing.

Inclusion of cefiderocol on the WHO Model List of Essential Medicines is being requested for the following reasons:

- Antimicrobial resistance is a growing problem worldwide and patients are in need of novel antibacterial options
- Cefiderocol offers coverage of multidrug-resistant, Gram-negative pathogens that other listed antibiotics have no – or limited – activity against
- Cefiderocol has a safety profile consistent with other cephalosporins.

2. Relevant WHO technical department and focal point (if applicable)

The Department of Health Products Policy and Standards and the Global Coordination and Partnership AMR Department.

3. Name of organization consulted and /or supporting the application

Shionogi & Co., Ltd.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

INN: Cefiderocol
ATC: J01D

5. Dose form(s) and strength(s) proposed for inclusion; including adult and age-appropriate pediatric dose forms/strengths (if appropriate).

Cefiderocol is supplied as a white to off-white, sterile, lyophilized powder for reconstitution in single-dose, clear glass vials. Each vial contains cefiderocol sulfate tosylate equivalent to 1 g of cefiderocol. The powder should be reconstituted with 10 mL of either sodium chloride 9 mg/ml (0.9%) solution for injection or 5% dextrose injection taken from the 100 mL bags that will be used to prepare the final infusion solution and should be gently shaken to dissolve. The final volume of the reconstituted solution in the vial will be approximately 11.2 mL (2, 3).

The recommended dosage of cefiderocol is 2 grams administered every 8 hours by intravenous (IV) infusion over 3 hours in adults with a creatinine clearance (CLcr) of 60 to 119 mL/min. Dosage adjustment of cefiderocol is recommended for patients with CLcr less than 60 mL/min, including patients receiving intermittent hemodialysis or continuous renal replacement therapy, and for patients with CLcr 120 mL/min or greater. The recommended duration of treatment with cefiderocol is 7 to 14 days. The duration of therapy should be guided by the patient's clinical status.

Cefiderocol is currently marketed in the United Kingdom (UK) and Germany (as FETCROJA) and the United States (US) (as FETROJA).

Cefiderocol is currently being investigated in pediatric populations in the US (NCT04215991/EudraCT 2019-002121-30) and the EU (NCT04335539/EudraCT 2019-002120-32). These phase 2 studies will evaluate the safety, tolerability and PK of cefiderocol in patients who are 3 months to less than 18 years of age and have Gram-negative bacterial infections or cUTI.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

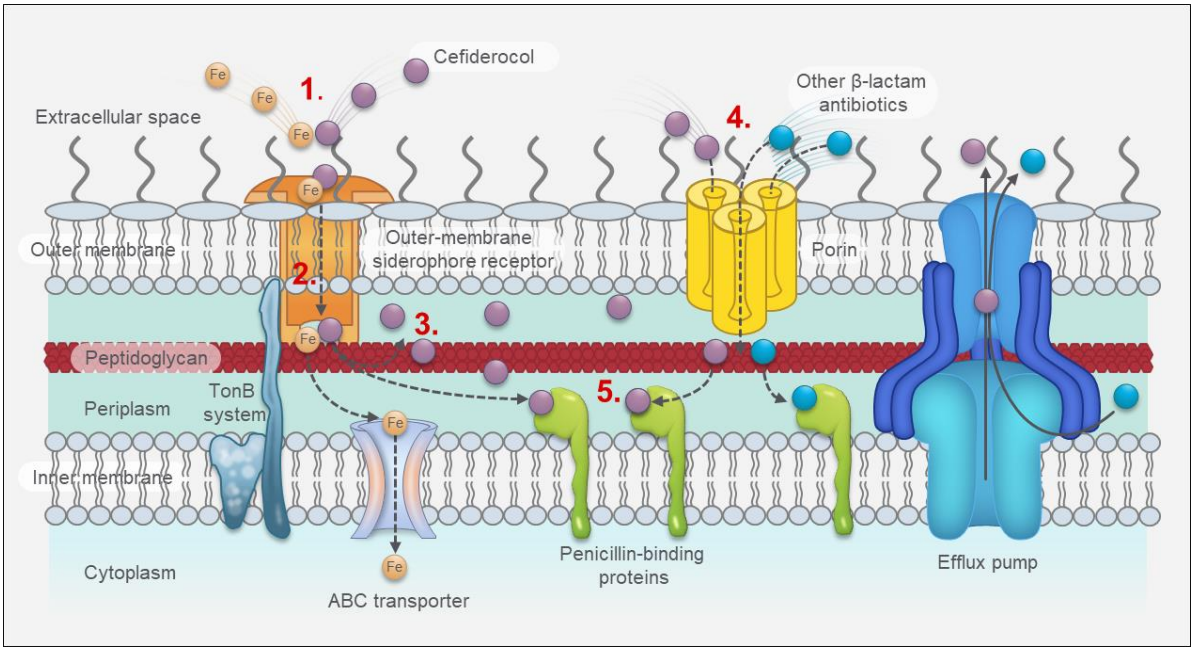
Cefiderocol is being requested as an individual medicine within the Reserve Group Antibiotics.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

Therapeutic dosage regimen of treatment

Cefiderocol is a parenteral siderophore cephalosporin antibiotic discovered and developed by Shionogi. In addition to passive diffusion through outer membrane porin channels (4 in Fig. 1), cefiderocol can bind to extracellular free iron via its siderophore side chain (1 in Fig. 1), allowing active transport into the periplasmic space of Gram-negative bacteria through siderophore uptake systems (2 in Fig. 1). This mechanism allows for higher concentrations of cefiderocol in the bacteria than with passive diffusion alone and enables entry even with porin channel mutations. Once across the outer membrane, the iron dissociates (3 in Fig. 1), and cefiderocol subsequently binds to penicillin binding proteins (PBPs), inhibiting bacterial peptidoglycan cell wall synthesis which leads to cell lysis and death (5 in Fig. 1).

Figure 1: Cefiderocol mechanism of action (from Morgan et. al. (4))



Cefiderocol is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options in the EU, where it is recommended that cefiderocol should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases. The EU label is pathogen-focused, allowing for flexibility in prescribing for different sites of infection. Combined with diagnostic testing, the label also supports appropriate use.

In the US, cefiderocol is indicated for adult patients with cUTI or HABP/VABP caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex or *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*, respectively. Administration and dosing are described in Table 1.

Table 1. Administration and dosing of cefiderocol

Method of administration	Intravenous use; administered by intravenous infusion over 3 hours.
Doses	1 g/vial; the recommended dose for individuals with normal renal function is 2g over 3h infusion
Dosing frequency	Every 8 hours (three times daily) for individuals with normal renal function
Average length of a course of treatment	Overall duration of treatment is in accordance with the site of infection.
Anticipated average interval between courses of treatments	Each treatment cycle lasts 8 hours; 3h of infusion and then 5h until the next cycle begins.

Anticipated number of repeat courses of treatments	For complicated urinary tract infections including pyelonephritis, the recommended treatment duration is 5 to 10 days. For hospital-acquired pneumonia, including ventilator-associated pneumonia, the recommended treatment duration is 7 to 14 days. Treatment up to 21 days may be required.
Dose adjustments	Dose adjustments are necessary for patients with renal impairment (reduced dose) or augmented renal function (increased dose). It is recommended that patients with ¶ CLcr 30 to 59ml/min be dosed with 1.5g cefiderocol infused over 3h every 8h ¶ CLcr 15 to 29mL/min be dosed with 1g cefiderocol infused for 3h every 8h ¶ CLcr less than 15mL/min be dosed with 0.75g cefiderocol infused over 3h every 12h ¶ CLcr greater than or equal to 120mL/min be dosed with 2.0g cefiderocol infused over 3h every 6h

Reference WHO guidelines and/or other evidence-based clinical guidelines

Clinical guidelines are developed for treatment of bacterial-associated indications based on location of infection or pathogen type. In many cases, there is not a single standard of care because treatment will need to be tailored to the type of pathogen. Recommendations refer either to most common infection sites (e.g. pneumonia, sepsis, cUTI) or, more recently, to pathogen types, e.g., infections with multidrug-resistant (MDR)/carbapenem-resistant (CR) Gram-negative bacteria (5-8) or more specificly, ESBL-producing bacteria or CR bacteria (9).

Fewer guidelines refer to specific treatments (10, 11). As clinical data are rare, recommendations are often based on evidence derived from in vitro susceptibility testing results, case studies, observational studies and expert opinion, which is standard and the most appropriate approach in antimicrobial treatment decisions. In general, all guidelines recommend that appropriate treatment should be started early (within hours) for patients who are vulnerable to infection or with suspected infections, and these guidelines often support the antibacterial de-escalation strategy and recommend that empirical antibacterial therapy should be implemented in accordance with local microbiological data and previous treatment (12).

Cefiderocol is a newly approved antimicrobial drug, so is not yet included on many formal clinical guidelines. However, its utility against a number of critical pathogens has been recognized by both the WHO and the Infectious Diseases Society of America (IDSA) (13, 14).

Activity against pathogens on the WHO Priority Pathogen list is one measure of clinical benefit. In the WHO report, “2019 Antibacterial Agents in Clinical Development,” cefiderocol is identified as a siderophore cephalosporin that is active against a number of WHO priority pathogens, including extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, *Klebsiella pneumoniae* (*K. pneumoniae*) carbapenemase (KPC), and oxacillinase-48 (OXA-48)-producing *Enterobacteriaceae* (13).

Cefiderocol is also active against both MDR *Acinetobacter baumannii* (*A. baumannii*) and MDR *Pseudomonas aeruginosa* (*P. aeruginosa*), which is unique amongst antimicrobials in the current development pipeline. Further, this report noted that cefiderocol is intrinsically more stable to a variety of β-lactamases than other β-lactam agents.

In September 2020, the IDSA released "Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections". IDSA Clinical Guidance documents are developed based on a comprehensive (but not necessarily systematic) review of the available evidence, coupled with the experience of clinical and research experts on the topic. This guidance serves as an alternative and complement to comprehensive clinical practice guidelines (15). The IDSA guidance documents are meant to address specific clinical questions that are not covered by current guidelines. The September guidance focused on the treatment of infections caused by extended spectrum beta-lactamase (ESBL) *Enterobacterales*, carbapenem-resistant *Enterobacterales* (CRE), and *P. aeruginosa* with difficult-to-treat resistance (DTR) (14). In this IDSA guidance, written prior to FDA approval for HABP/VABP, cefiderocol is recommended as a preferred treatment for:

- Pyelonephritis and cUTIs caused by CRE or DTR-*P. aeruginosa*
- Infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem, when carbapenemase testing results are either not available or negative and the patient has recently traveled from an area where metallo-β-lactamases are endemic
    - Cefiderocol is an alternative treatment option for infections outside the urinary tract caused by DTR-*P. aeruginosa*
- Infections outside of the urinary tract caused by CRE with NDM or other metallo-β-lactamase production
- Uncomplicated cystitis caused by DTR-*P. aeruginosa*

Consideration of any additional requirements associated with treatment, such as diagnostics, specialized treatment facilities, administration, monitoring, etc.

The use of cefiderocol is for hospital use only, and is not expected to require any specialized equipment, or to demand additional resources beyond the standard ability to store, prepare and administer intravenous infusion treatments. Susceptibility testing to cefiderocol and standard monitoring microbiological evaluation tests are also needed, as is current practice with all hospital use antibacterials in nosocomial infections.

Cefiderocol should be stored in a refrigerator at 2°- 8°C and should be protected from light. Chemical, microbiological and physical in-use stability after dilution has been demonstrated for 6 hours at 25°C and for 24 hours at 2 to 8°C protected from light, followed by 6 hours at 25°C.

8. Information supporting the public health relevance.

Epidemiological information on the burden of antimicrobial resistance

Antimicrobial resistance (AMR) is a major, and growing, threat to global public health. Treatment of pathogens has become more and more challenging due to the emergence of resistance, especially to

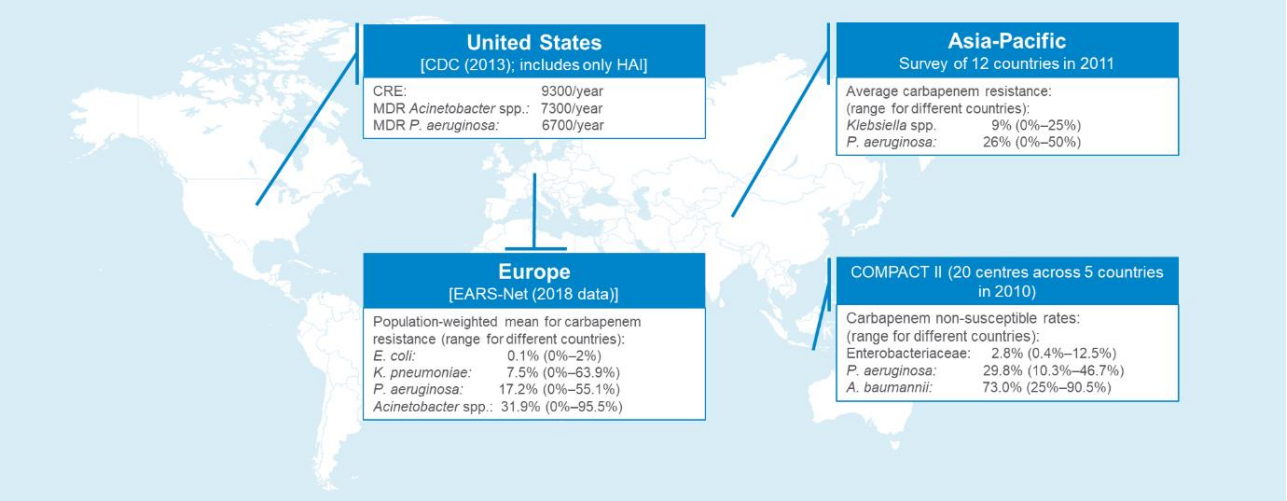
carbapenems which are usually reserved for use where other options have failed (1, 16-21). AMR is estimated to contribute to 700,000 deaths every year globally (22-24). If significant action is not taken, it is estimated that 10 million lives will be lost each year to AMR by 2050 (22). The WHO has identified CR *A. baumannii*, CR *P. aeruginosa*, and CR, ESBL-producing Enterobacteriaceae as the most critical pathogens in need of new antibiotics (1).

Gram-negative pathogens are challenging to treat due to their potential intrinsic resistance to antibacterials and the emergence of acquired resistance, including metallo- and serine β-lactamase production, porin channel mutations, and efflux pump mechanisms (16). Non-fermenters such as *P. aeruginosa, A. baumannii,* and S. *maltophilia*, are often resistant to a large number of antibacterial treatments and also differ in their pathogenic potential and transmissibility (25).

Nosocomial infections primarily occur in vulnerable hospitalized patients. These patients are often over 50 years of age, likely to be severely ill, and generally have multiple comorbidities (26, 27). Infections caused by MDR pathogens, including Gram-negative organisms, can occur at many sites including the urinary tract, lungs, bloodstream, and abdominal tract.

The rate of infections caused by MDR bacteria continues to increase and limit the utility of existing antibacterial agents. Reports on CR isolates are highly heterogeneous across the globe (Figure 2), but the prevalence of carbapenem resistance has been found to be particularly high in Mediterranean countries, South America and Asia-Pacific countries, with the exception of Japan (28, 29).

Figure 2. Worldwide carbapenem resistance



Source: CDC 2013(24); ECDC 2017(21); Mendes et al.(30); Kiratisin et al.(31)

In its 2018 surveillance report, the European Centre for Disease Prevention and Control (ECDC) reported an increase in resistance to currently available treatments across some Gram-negative pathogens between 2015 and 2018 (32). ECDC estimate that nearly 700,000 infections and 33,000 deaths in the EU and European Economic Area (EEA) in 2015 are a consequence of MDR bacterial infections (23). CR in *P. aeruginosa*, *K. pneumoniae* and *Acinetobacter* spp. contributed significantly to the number of estimated

deaths (in total approximately 9,000 deaths). Across the EU-5 countries (France, Germany, Italy, Spain, United Kingdom), prevalence of CR Gram-negative infections ranges between 0.14 per 100,000 in the UK to 3.05 per 100,000 in Italy (Table 2) (23). While there appears to be geographical variation in different types of carbapenemases, a recent surveillance study reports an overall increase in these enzymes (29, 33).

Table 2. Prevalence of CR Gram-negative infections in the EU-5

EU-5 Country	Prevalence (Cases/100,000)
France	1.20
Germany	0.31
Italy	3.05
Spain	0.64
United Kingdom	0.14
EU-5 Average	1.07

The United States (US) experiences more than 2.8 million antibiotic-resistant infections each year, resulting in over 35,000 deaths (34). In their 2019 Antibiotic Resistant Threat Report, the US Centers for Disease Control and Prevention (CDC) described the prevalence of several priority pathogens in the US (Table 3).

Table 3. Estimated Disease Burden Due to Priority Pathogens in the US (Adapted from AR Threat Report)

Resistant bacteria	Estimated infections	Estimated deaths	Source of data
Drug-resistant *Neisseria gonorrhoeae*	550,000	N/A	All infections
ESBL-producing *Enterobacteriaceae*	197,400	9,100	Incident hospitalized Positive clinical cultures, including hospital- & community-onset
Erythromycin-resistant group A *Streptococcus*	5,400	450	Invasive infections
Carbapenem-resistant *Enterobacteriaceae*	13,100	1,100	Incident hospitalized positive clinical cultures, including hospital- & community-onset
Carbapenem-resistant *Acinetobacter*	8,500	700	Incident hospitalized positive clinical cultures, including hospital- & community-onset
Vancomycin-resistant *Enterococcus*	54,500	5,400	Incident hospitalized positive clinical cultures, including hospital- & community-onset
Multidrug-resistant *Pseudomonas aeruginosa*	32,600	2,700	Incident hospitalized positive clinical cultures, including hospital- & community-onset
Methicillin-resistant *Staphylococcus aureus*	323,700	10,600	Incident hospitalized positive clinical cultures, including hospital- & community-onset
Drug-resistant Tuberculosis	847	62	Cases
Clostridioides difficile	223,900	12,800	Infections requiring hospitalizations or in already hospitalized patients
Drug-resistant *Campylobacter*	448,400	70	All infections
Drug-resistant nontyphoidal *Salmonella*	212,500	70	All infections
Drug-resistant *Salmonella* Serotype Typhi	4,100	<5	All infections
Drug-resistant *Shigella*	77,000	<5	All infections
Drug-resistant *Streptococcus pneumoniae*	900,000	3,600	All infections
Clindamycin-resistant group B *Streptococcus*	13,000	720	Invasive infections

Comprehensive epidemiology data are incomplete in many nations where surveillance infrastructure is lacking. Using a compilation of sources, the Center for Disease Dynamics, Economics & Policy has created estimates of AMR rates world-wide (35). Figures 3-6 show the estimated percent of resistant isolates occurring in Asian, Latin American, Middle Eastern and African countries. Broad resistance of *A. baumanni, P. aeruginosa,* Enterobacteriaceae, and *K. pneumoniae* isolates to standard antibiotic treatments is evident throughout these regions.

Figure 3. Aggregated resistance rates of *A. baumannii* to carbapenems, fluoroquinolones or ceftazidime

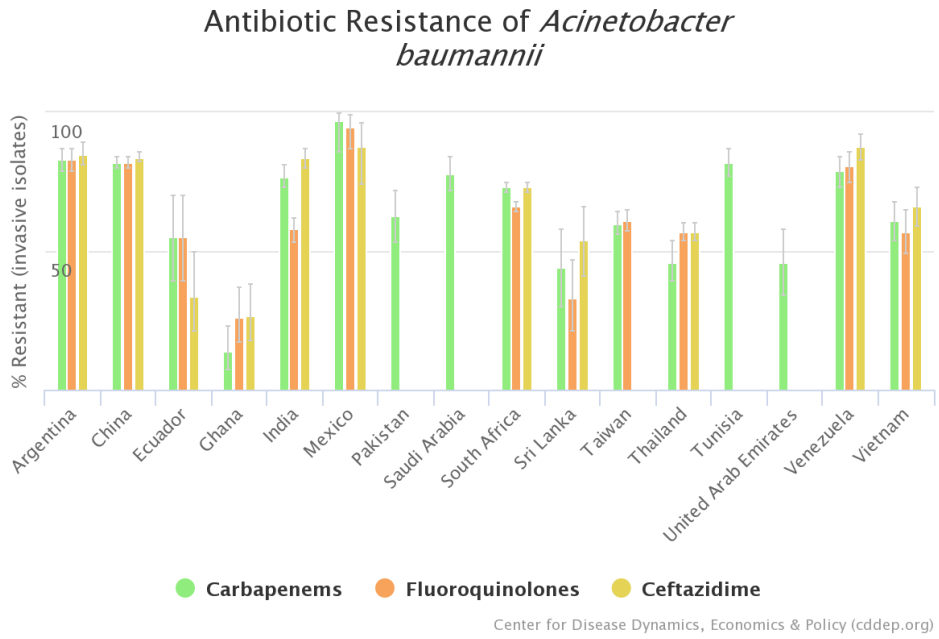


Figure 4. Aggregated resistance rates of *P. aeruginosa* to ceftazidime, fluoroquinolones or carbapenems

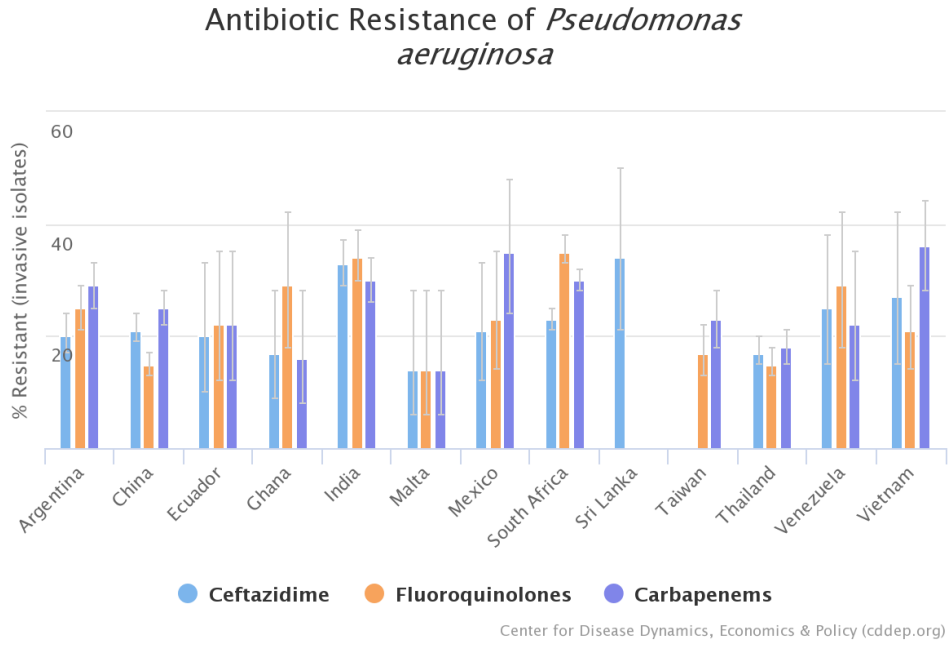


Figure 5. Aggregated resistance rates of *Enterobacter aerogenes/cloacae* to fluoroquinolones, piperacillin-tazobactam, cephalosporins (3rd gen) or carbapenems

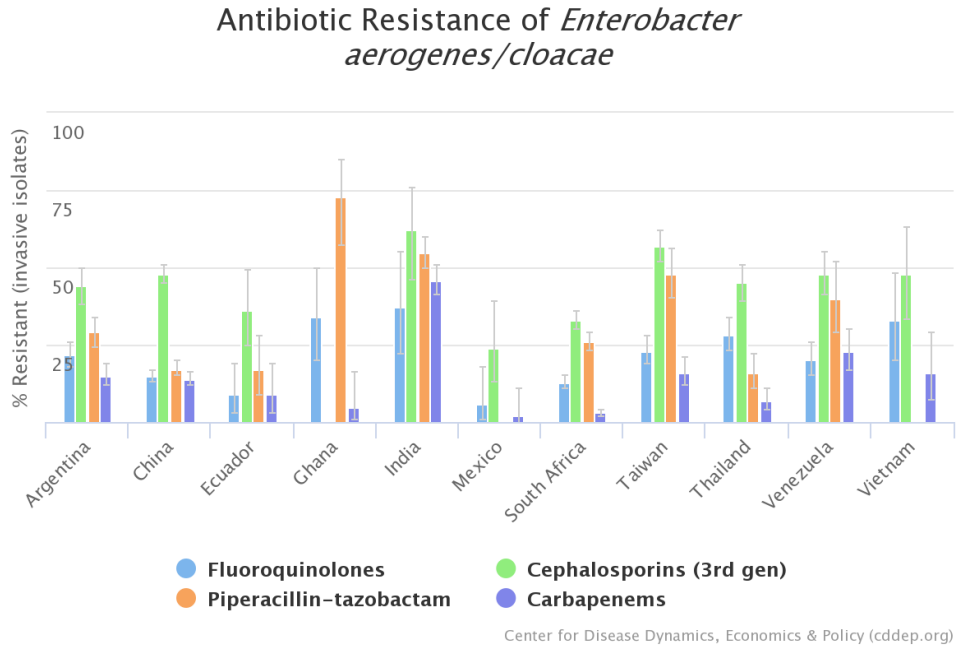
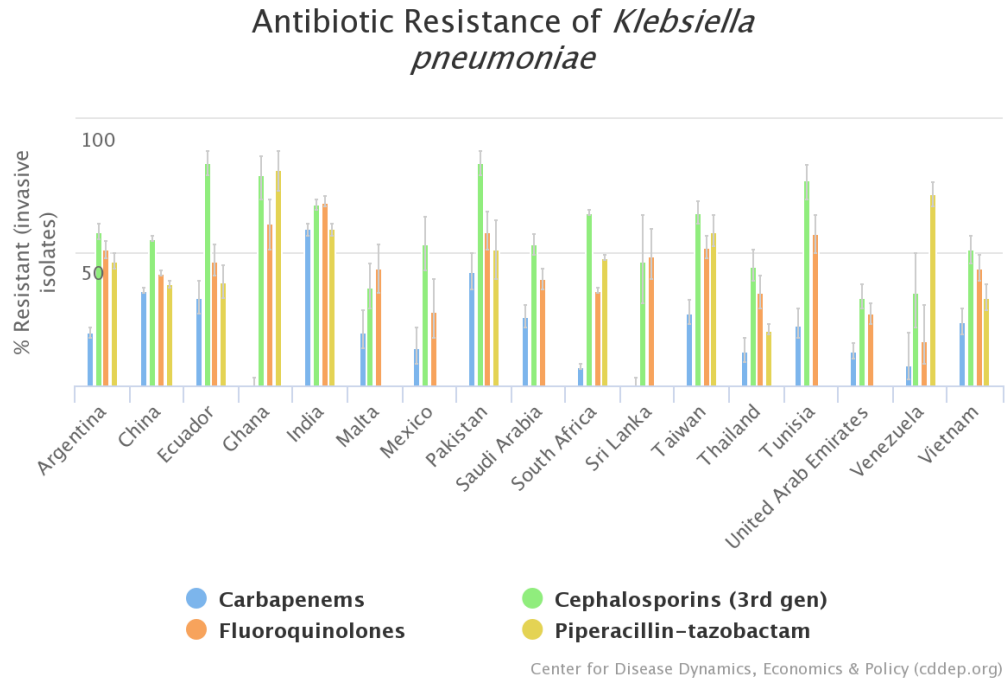


Figure 6. Aggregated resistance rates of *K. pneumoniae* to carbapenems, fluoroquinolones, cephalosporins (3rd gen) or piperacillin-tazobactam



Assessment of current use

Cefiderocol is commercially available in the UK, Germany and US. Prior to marketing, cefiderocol was studied in over 700 patients through clinical studies.

In addition to experience in clinical trials and post-approval patient access, compassionate use programs have been in place since 2016. Approximately 300 requests for cefiderocol have been received through these programs and 184 have been granted product. While the compassionate use program ended in the US upon -commercial availability of cefiderocol, cefiderocol is still provided through compassionate use programs in Europe, the Asia Pacific region and Canada (Special Access Programme) for qualified patients who have limited treatment options and are not eligible for a clinical trial. The criteria for compassionate use of cefiderocol were highly restrictive and cefiderocol was used in patients with serious infections, most often due to CR non-fermenters, and with limited or no alternative options.

Target population(s)

In Europe, cefiderocol is branded as "FETCROJA" and the indication is: "Fetcroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options."(3) This indication is pathogen focused, not restricted to any specific site of infection.

In the United States, cefiderocol is branded as "FETROJA" and approved for the treatment of cUTI and for the treatment of HABP and VABP. The "Indications" section of the FDA label is copied here (2):

- FETROJA is indicated in patients 18 years of age or older 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
- FETROJA is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*

Likely impact of treatment on the disease

Treatment options for infections with MDR/CR aerobic Gram-negative pathogens are very limited. For patients with limited treatment options, cefiderocol is the only antimicrobial with demonstrated in vitro activity against a broad set of pathogens such as CR *A. baumannii*, CR *P. aeruginosa, S. maltophilia*, and CR *Enterobacteriaceae* (Figure 7) (36, 37). As a result, cefiderocol is estimated to provide better predicted susceptibility rates and projected clinical success rates with a safety profile consistent with other cephalosporins.

Figure 7. Antibacterial β-lactamase-producing pathogens

	Nonfermenters					Fermenters		
	P. aeruginosa			*A. baumannii*	*S. maltophilia*	Enterobacteriaceae		
	Serine-carbapenemases	Metallo-carbapenemases	Other resistance mechanisms		Intrinsic carbapenem resistance	β-lactamases (including ESBLs)	Serine-carbapenemase	Metallo-carbapenemase
Cefiderocol	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ceftolozane-tazobactam	🔴	🔴	🟢	🔴	🔴	🟢	🔴	🔴
Ceftazidime-avibactam	🟡	🔴	🟡	🔴	🔴	🟢	🟢	🔴
Meropenem- vaborbactam	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🔴
Eravacycline	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Plazomicin	🟡	🟡	🟡	🟡	🔴	🟢	🟢	🟡
Relebactam-imipenem/cilastatin	🟡	🔴	🟡	🔴	🔴	🟢	🟢	🔴
Colistin	🟢	🟢	🟢	🟢	🟡	🟢	🟡	🟡

*Color-coding based on the pathogen susceptibility: Green – Activity reported, yellow – undetermined activity reported, and red – no clinically relevant activity reported. Source: Thalhammer F, 2018 (38), Theuretzbacher, 2019 (39)

9. Review of benefits: summary of evidence of comparative effectiveness

Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion)

To identify all relevant studies for cefiderocol and comparators, a comprehensive systematic literature review was conducted comprising in vitro and in vivo studies, as well as any comparative or non-comparative studies and registered clinical trials (RCTs) (including cross-over RCTs); 153 records were included in the reference set. Full search details are included in Appendix A.

The comparative evidence included in this application were derived from in vitro surveillance studies and RCTs. As has been discussed in several publications, it is unethical to include in antibiotic clinical trials patients with infections that are known to be resistant to the comparator treatment, necessitating a non-inferiority design (40-43). In addition, antibiotic products may face challenges with enrollment and evidence analysis because (44, 45):

- Immediate treatment is necessary for serious bacterial diseases, so patients may receive antibiotic therapy before trial enrollment, potentially obscuring the effect of the experimental antibiotic.
- There may be diagnostic uncertainty with respect to the aetiology of the patients' underlying disease, including pathogen identification.
- There may be a need for concomitant antibacterial drug therapy with a spectrum of activity that may overlap with the antibacterial drug being studied.
- MDR/CR pathogens are still relatively rare in individual hospitals, so a trial to evaluate specific types of resistance would require the screening and recruitment of a prohibitively large number of people.
- A comparison of efficacy against all relevant comparators can only be obtained from in vitro surveillance studies.

Despite these challenges, cefiderocol was demonstrated to have in vitro activity against a number of MDR and CR pathogens, including those found on the WHO Priority Pathogen list: CR *A. baumannii,* CR

P. aeruginosa, and MDR Enterobactericeae. Cefiderocol was also found to be non-inferior to imipenem/cilastatin in the treatment of cUTI; non-inferior to high-dose, prolonged infusion (2g administered over 3hr) meropenem for treatment of HABP/VABP; and an effective treatment against infections caused by a broad set of aerobic, CR Gram-negative pathogens (46-48).

Each clinical study used its own comparator and was conducted in different patient populations. For this reason, no overall results summary table is shown here. However, a recent systematic review and meta-analysis compared the efficacy and safety of new antibiotics to carbapenems for the treatment of cUTI. The pooled efficacy estimates of composite cure favored the new antibiotics, including cefiderocol, over carbapenem, and found that new antibiotics were superior to carbapenems in microbiological response (49).

The quality of the two randomized, controlled, double-blinded studies (APEKS-cUTI and APEKS-NP) and the randomized, open-label, non-inferential study (CREDIBLE-CR) was assessed to demonstrate the efficacy and safety profiles. Using the GRADE assessment system, the analysis concluded that the APEKS studies were of high quality with low risk of bias and the CREDIBLE-CR study was of moderate quality (Table 4).

Table 4. GRADE quality assessment for the cefiderocol clinical trials

Study	Type of study: RCT = high quality	Lack of allocation concealment	Lack of blinding	Incomplete accounting of patients and outcome events	Selective outcome reporting	Other limitations	GRADE for study
APEKS-cUTI	High quality	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	4
APEKS-NP	High quality	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	4
CREDIBLE -CR	Low quality	high risk of bias	high risk of bias	low risk of bias	Low risk of bias	Low risk of bias	2

Summary of available data and estimates of comparative effectiveness

Individual study results (in vitro surveillance outcomes)

The in vitro activity of cefiderocol was studied in large-scale, multinational surveillance and small, independent national studies (50). The following section describes the multinational surveillance analyses, SIDERO-WT and SIDERO-CR.

1a) SIDERO-WT results for all Gram-negative isolates (50-52)

The SIDERO-WT analysis (study report S-649266-EB-344-N) was an extensive effort to determine activity of cefiderocol and relevant comparators against cabapenem-susceptible and carbapenem-resistant pathogens. Cefiderocol MICs were determined and compared to a panel of relevant antibacterials using breakpoints from the Clinical & Laboratory Standards Institute (CLSI) (37, 50-53). The cefiderocol MIC of 4µg/mL was consistent with the CLSI breakpoints published in 2019 and those derived from PK/PD and PK analyses in clinical studies. However, subsequently published European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for cefiderocol are lower, set as 2mg/L for *Enterobacterales*

and *Pseudomonas aeruginosa* and not determined for *Acinetobacter* spp (54). FDA lists breakpoints for cefiderocol as ≤4µg/mL for Enterobacteriaceae and ≤1µg/mL for *P. aeruginosa* and *A. baumannii* complex (55). Within the SIDERO studies, using the lower FDA and EUCAST breakpoints results in some isolates shifting from cefiderocol-susceptible to resistant (56). In the clinical context, these lower breakpoints may have negative consequences for the care of patients with multidrug resistant infections, which may be incorrectly labeled as resistant to cefiderocol.

Cefiderocol demonstrated activity against the majority of Gram-negative isolates tested at MIC of <4 µg/mL (only MIC_{90} for *B. multivorans* was 32 µg/mL) and had higher coverage rates than other examined comparators (50). To date, 30,459 samples have been tested, with testing of 9,205 Gram-negative bacterial clinical isolates in 2014–2015, 8,954 in 2015–2016, and 10,470 in 2016–2017 (50). Cefiderocol was effective at low MICs for more than 99% of isolates in each testing period (50). The latest surveillance SIDERO-WT study (2016-2017) showed that cefiderocol demonstrated activity against 99.45% of Gram-negative pathogens at MIC of 4µg/mL compared to 90.2% for ceftazidime-avibactam, 84.28% for ceftolozane-tazobactam, and 95.49% for colistin (Table 5) (51).

Table 5: Percent of isolates with in vitro susceptibility to cefiderocol, colistin, ceftolozane-tazobactam and ceftazidime-avibactam

Organism	Cefiderocol	Polymyxin E (colistin)	Ceftolozane/ tazobactam	Ceftazidime/ avibactam
All Gram-negative (n=30,459)	99.45	95.49[b] (n=25372)	84.28	90.20
Enterobacteriaceae (n=20,949)	99.86	96.54[c] (n=16026)	91.43	99.23
Non-fermenters[a] (n=9,510)	98.53	93.67[d] (n=9346)	68.52	70.33
CR *Enterobacteriaceae* (n=654) (MEPM MIC ≥ 2 µg/mL)	98.16	75.55[c] (n=581)	8.40	77.67
CR Non-fermenters (n=4,331) (MEPM MIC ≥ 4 µg/mL)	97.57	86.85[d] (n=4208)	34.61	40.96
CR *P. aeruginosa* (n=1,154) (MEPM MIC ≥ 4 µg/mL)	99.91	98.35	76.08	75.38
CR *A. Baumannii* (n=1,891) (MEPM MIC ≥ 4 µg/mL)	94.87	85.14	7.77	16.23
S. maltophilia (n=1,173)	99.82	78.17	34.27	42.88

Source: (51). MEPM - meropenem; MIC - minimum inhibitory concentration. Green: More than 80% susceptible; yellow: between 60-80% susceptible, red: less than 60% susceptible. Data reflect all tested clinical strains (SIDERO-WT-2014/2015/2016 and Proteeae). Ratios (%) susceptible strains were calculated by using the following MIC criteria: Cefiderocol MIC ≤4 µg/mL, ceftazidime/avibactam MIC ≤8 µg/mL, ceftolozane/tazobactam MIC ≤2 µg/mL for *Enterobacteriaceae*, ≤4 µg/mL for non-fermenters, colistin MIC ≤2 µg/mL.

[a] Non-fermenters include *P. aeruginosa*, *S. maltophilia*, *Burkholderia* spp, and *Acinetobacter* spp.

[b] *Burkholderia* spp, *Proteeae* and *Serratia* spp. were excluded because they are intrinsically resistant to Polymyxin E (Colistin)
[c] *Serratia* spp. and *Proteeae* was excluded.
[d] *Burkholderia* spp was excluded.

1b) SIDERO-WT-based analysis of difficult-to-treat resistant (DTR) pathogens (57)

A subsequent analysis focused on a DTR subset of pathogens, which were non-susceptible to fluoroquinolones, extended-spectrum cephalosporins, and carbapenems (57). The results from this analysis showed that cefiderocol demonstrated potent activity against DTR Gram-negative pathogens. Pathogens were defined as DTR if they were non-susceptible to fluoroquinolones (ciprofloxacin), extended-spectrum cephalosporins (cefepime) and carbapenems (meropenem) according to CLSI M100-E28:2018 breakpoints (Table 6). *Stenotrophomonas maltophilia* was considered inherently non-susceptible to carbapenems, however, an arbitrary breakpoint of >4 µg/mL was used. Among 30,459 Gram-negative isolates collected between 2014 and 2017, 9.3% were non-susceptible to cefepime, ciprofloxacin and meropenem and could be defined as DTR.

Table 6. Breakpoints for non-susceptibility used in definition of

Organism	Cefepime	Ciprofloxacin	Meropenem
Enterobacterales	>2	>1	>1
P. aeruginosa	>8	>1	>2
A. baumannii	>8	>1	>2
S. maltophilia	>8*	>1*	>4*
B. cepacia complex	>8*	>1*	>4

*No approved CLSI breakpoints available so above arbitrary cut-offs used

The DTR phenotype was most frequently observed in *Acinetobacter* spp. (55.5%), followed by *Burkholderia* spp. (19%), *Pseudomonas aeruginosa* (9.5%) and Enterobacterales (2.7%). Cefiderocol demonstrated activity in 94.5% of DTR *A. baumannii*, 99.8% of *P. aeruginosa* and 98.3% of *Enterobacterales* (58). These pathogens were less susceptible to other available treatments (Table 7) (58).

Table 7. Percent of isolates with in vitro susceptibility to cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam and colistin

Pathogen	Cefiderocol[a]	Ceftazidime / avibactam[a]	Ceftolozane / tazobactam[a]	Colistin[a]
DTR *Enterobacterales* (n=573)	98.3	78.2	2.05	68.2
DTR *P. aeruginosa* (n=470)	99.8	49.5	48.8	98.3
DTR *A. baumannii* (N=3,451)	94.5	14.2	5.8	85

In addition, 98.7% of carbapenem-non-susceptible (CarbNS) Enterobacteriaceae, and 96.4% of CarbNS non-fermenters were found to be sensitive to cefiderocol at a MIC of ≤4µg/mL (Table 8).

Table 8. Percent of isolates with in vitro susceptibility to cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam and colistin

Pathogen	Cefiderocol[a]	Ceftazidime / avibactam[a]	Ceftolozane / tazobactam[a]	Colistin[a]
CarbNS[b] *Enterobacteriaceae* (225)	98.7	81.3	11.1	71[d]
CarbNS[b] non-fermenters[c] (n=1427)	96.4	39.8	37.0	91.5[e]
CarbNS[b] *P. aeruginosa* (n=406)	100	75.6	77.3	97.3
CarbNS[b] *A. baumannii* (n=565)	91	11.0	9.0	90.8
S. maltophilia (n=405)	100	38.8	31.4	86

CarbNS, carbapenem-non-susceptible
[a] Ratios (%) susceptible strains were calculated by using the following MIC criteria: Cefiderocol MIC ≤4 µg/mL, ceftazidime/avibactam MIC ≤8 µg/mL, ceftolozane/tazobactam MIC ≤2 µg/mL for *Enterobacteriaceae*, ≤4 µg/mL for non-fermenters, colistin MIC ≤2 µg/mL.
[b] CR strain was defined as meropenem MIC ≥2 µg/mL for *Enterobacteriaceae*, ≥4 µg/mL for non-fermenters
[c] Non-fermenters include *P. aeruginosa*, *S. maltophilia*, *Burkholderia* spp, and *Acinetobacter* spp.
[d] *Serratia spp.* and *Proteeae* were excluded.
[e] *Burkholderia spp.* was excluded.
Source: Tsuji 2019(51)

2) SIDERO-CR-2014-2016 study (protocol S-649266-EF-115-N)

The SIDERO-CR-2014-2016 study (protocol S-649266-EF-115-N) collected CR isolates and MDR non-fermenters from Europe, North America, South America, and the Asia-Pacific region. Cefiderocol demonstrated potent in vitro activity against all of these pathogens (36).

In this study, cefiderocol had in vitro activity at a MIC_{90} between 0.25 - 8µg/mL against CR Enterobacteriaceae and MDR non-fermenters (defined as resistant to carbapenems, fluoroquinolones, and aminoglycosides) (36, 50). For MIC of ≤ 4µg/mL, cefiderocol was active against 96.2% of these pathogens, which was a higher efficacy than other available treatments (36, 50). Cefiderocol inhibited the growth of 97.0% of CR Enterobacteriaceae, 99.2% of MDR *P. aeruginosa*, 90.9% of MDR *A. baumanii* and 100% of *S. maltophila* isolates at a concentration of 4µg/mL (Table 9) (36, 50).

Table 9. Percent of isolates with in vitro susceptibility to cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam and colistin

Pathogen	Cefiderocol[a]	Ceftazidime / avibactam[a]	Ceftolozane / tazobactam[a]	Colistin[a]
CarbNS[b] *Enterobacteriaceae* (n=1022)	97.0	77.0	1.7	77.8[c]
MDR *P. aeruginosa* (n=262)	99.2	36.3	24.1	99.6
MDR *A. baumannii* (n=368)	90.9	NA	NA	94.6
S. maltophilia (n=217)	100	NA	NA	NA

CarbNS, carbapenem-non-susceptible; MDR, multi drug resistant; NA, susceptibility breakpoints not available
a Ratios (%) susceptible strains were calculated by using the following MIC criteria: Cefiderocol MIC ≤4 µg/mL, ceftazidime/avibactam MIC ≤8 µg/mL, ceftolozane/tazobactam MIC ≤2 µg/mL for *Enterobacteriaceae*, ≤4 µg/mL for non-fermenters, colistin MIC ≤2 µg/mL.
b CR strain was defined as meropenem MIC ≥2 µg/mL for *Enterobacteriaceae*, ≥4 µg/mL for non-fermenters
c Includes 39 Serratia species that are intrinsically resistant to colistin
Source: Hackel, 2018 (36); Yamano (50)

In addition to the high activity of cefiderocol against different drug-resistant species, the SIDERO-CR study showed that cefiderocol had activity against isolates with previously characterized resistance factors, including VIM-, NDM-, KPC-, and OXA-producing *Enterobacteriaceae*, VIM-producing *P. aeruginosa,* MEPM-non-susceptible but acquired β-lactamase negative *P. aeruginosa,* OXA-23 and OXA-24/40 carbapenemase-producing *A. baumannii*.

Clinical study results (clinical outcomes)

In addition to in vitro studies, a number of clinical studies were conducted to demonstrate the efficacy and safety of cefiderocol in patients with bacterial infections. Three phase 2 and phase 3 studies will be discussed here: APEKS-cUTI, APEKS-NP and CREDIBLE-CR (46-48).

APEKS-cUTI

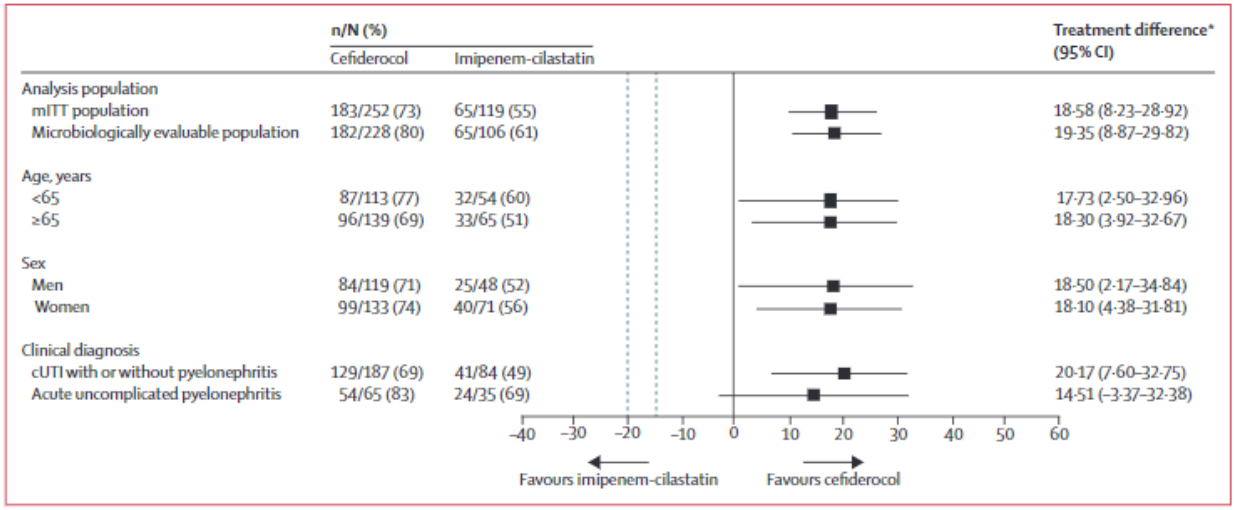
APEKS-cUTI was a Phase 2, multi-center (multinational), double-blind, randomized, active-controlled, parallel-group study conducted in hospitalized adult subjects with cUTIs with or without pyelonephritis or acute uncomplicated pyelonephritis caused by Gram-negative pathogens. This study assessed the efficacy and safety of intravenous cefiderocol (2g over 3hr every 8 hr) in comparison with intravenous, high-dose (2g over 3hr every 8 hr) imipenem/cilastatin (IPM/CS) and included 452 patients diagnosed with complicated urinary tract infections (46) (Clinicaltrials.gov Record NCT02321800).

The primary efficacy endpoint was the composite of clinical outcome and microbiological outcome at test of cure (TOC). The response rate for the primary efficacy endpoint was 73% (183/252) of patients in the cefiderocol group and 55% (65/119) of patients in the IPM/CS group (Figure 8). Cefiderocol met the criteria to demonstrate noninferiority with a prespecified 20% margin. Similar results were observed in

the sensitivity analysis (composite clinical and microbiological response in microbiologically-evaluable (ME) population) (46, 59). Results of this study are detailed in *Lancet Infectious Diseases* (46).

At TOC, clinical response was 89.7% (226/252) of patients in the cefiderocol group and 87.4% (104/119) of patients in the IPM/CS group. At follow up, sustained clinical response was higher in the cefiderocol group (81.3% [205/252] of patients) than in the IPM/CS group (72.3% [86/119] of patients), with an adjusted treatment difference of 9.02% (95% CI; -0.37%, 18.41%) (Table 10).

Figure 8. Primary efficacy results: Composite outcome at TOC by predefined subgroups



Portsmouth et. al. (46). mITT= modified intention-to-treat. Dotted lines represent prespecified non-inferiority margins at -20% and -15%.

Table 10. Summary of Microbiological and Clinical Outcomes per Subject by Time Point (from Portsmouth et. al. (46))

	Cefiderocol (n=252)	Imipenem-cilastatin (n=119)	Treatment difference, % (95% CI)
Microbiological outcome			
Early assessment			
Microbiological eradication	232 (92%)	108 (91%)	1·28 (−4·83 to 7·39)
Microbiological failure	14 (6%)	7 (6%)	..
Indeterminate	6 (2%)	4 (3%)	..
End of treatment			
Microbiological eradication	244 (97%)	114 (96%)	1·10 (−3·04 to 5·25)
Microbiological failure	3 (1%)	3 (3%)	..
Indeterminate	5 (2%)	2 (2%)	..
Test of cure			
Microbiological eradication	184 (73%)	67 (56%)	17·25 (6·92 to 27·58)
Microbiological failure	53 (21%)	44 (37%)	..
Indeterminate	15 (6%)	8 (7%)	..
Follow-up			
Sustained microbiological eradication	144 (57%)	52 (44%)	13·92 (3·21 to 24·63)
Microbiological failure	84 (33%)	42 (35%)	..
Indeterminate	24 (10%)	25 (21%)	..
Clinical outcome			
Early assessment			
Clinical response	228 (90%)	108 (91%)	−0·26 (−6·57 to 6·05)
Clinical failure	23 (9%)	10 (8%)	..
Indeterminate	1 (<1%)	1 (1%)	..
End of treatment			
Clinical response	247 (98%)	118 (99%)	−1·07 (−3·42 to 1·29)
Clinical failure	4 (2%)	0	..
Indeterminate	1 (<1%)	1 (1%)	..
Test of cure			
Clinical response	226 (90%)	104 (87%)	2·39 (−4·66 to 9·44)
Clinical failure	14 (6%)	8 (7%)	..
Indeterminate	12 (5%)	7 (6%)	..
Follow-up			
Sustained clinical response	205 (81%)	86 (72%)	9·02 (−0·37 to 18·41)
Clinical failure	19 (8%)	13 (11%)	..
Clinical relapse	12 (5%)	12 (10%)	..
Indeterminate	16 (6%)	8 (7%)	..

Data are n (%).

Table 2: **Microbiological and clinical outcomes in the modified intention-to-treat population**

The microbiological eradication rate in the modified intention-to-treat (mITT) population was significantly higher at TOC in the cefiderocol group (73.0% [184/252] of patients) compared with the IPM/CS group (56.3% [67/119] of patients). The adjusted treatment difference of 17.25% (95% CI; 6.92%, 27.58%) in favor of the cefiderocol group was statistically significant and clinically meaningful. Results for both treatment groups were similar at early assessment (EA) and at end of treatment (EOT). The sustained microbiological eradication rate at follow up (FUP) was also higher in the cefiderocol group (57.1% [144/252] of patients) compared with the IPM/CS group (43.7% [52/119] of patients). The adjusted treatment difference of 13.92% (95% CI; 3.21%, 24.63%) in favor of the cefiderocol group was statistically significant and clinically meaningful.

No new infections were noted during the study. Superinfection, defined as an uropathogen emerging during study drug therapy, was limited to a single occurrence of *E. coli* in one patient (Subject 143-002) in the cefiderocol group. The patient had *E. coli* isolated from the urine at the EA visit. Of note, this patient only had *P. aeruginosa* isolated at baseline and was treated for 10 days with cefiderocol. The *E. coli* superinfection was sensitive to levofloxacin, cefepime, and IPM, and the MIC for cefiderocol was 0.12 µg/mL. Both *E. coli* and *P. aeruginosa* were eradicated at TOC, and *P. aeruginosa* alone was isolated at FUP.

APEKS-NP study

The APEKS-NP study was a multi-center, double-blind, randomized, phase 3 clinical study comparing cefiderocol with high-dose (HD), extended-infusion meropenem for the treatment of HABP, VABP or HCABP caused by Gram-negative pathogens. The dose of meropenem was increased from the usual dose of 1 g to 2 g and extended to a 3-hour infusion to optimize the antibacterial activity of meropenem, at the request of regulators (60). Cefiderocol demonstrated non-inferiority to HD extended-infusion meropenem with regard to all-cause mortality at Day 14. Full study results were published in *The Lancet Infectious Disease* (47).

Of the 292 patients in the mITT population, 251 (86%) had a qualifying baseline Gram-negative pathogen, including *K. pneumoniae* (92 [32%]), *P. aeruginosa* (48 [16%]), *A. baumannii* (47 [16%]), and *Escherichia coli* (41 [14%]). One hundred forty-two (49%) patients had an APACHE II score of 16 or more, 175 (60%) were mechanically ventilated, and 199 (68%) were in intensive care units at the time of randomization. The all-cause mortality rate was 12.4% (18/145 subjects) for the cefiderocol group and 11.6% (17/146 subjects) for the high-dose (HD) meropenem group, demonstrating the noninferiority of cefiderocol, as the upper limit of the 95% CI was < 12.5% (95% CI: −6.6, 8.2) (Table 11).

Rates of microbiological eradication and clinical cure at TOC aligned with the primary outcome in that results were similar between the treatments (Table 12). The microbiological eradication at TOC was 47.6% (59/124) in the cefiderocol group and 48.0% (61/127) in the HD meropenem group, and the clinical cure at TOC was 64.8% (94/145) in the cefiderocol group and 66.7% (98/147) in the HD meropenem group.

Table 11. Day 14 All-cause Mortality (mITT population) (from Wunderink et. al. (47))

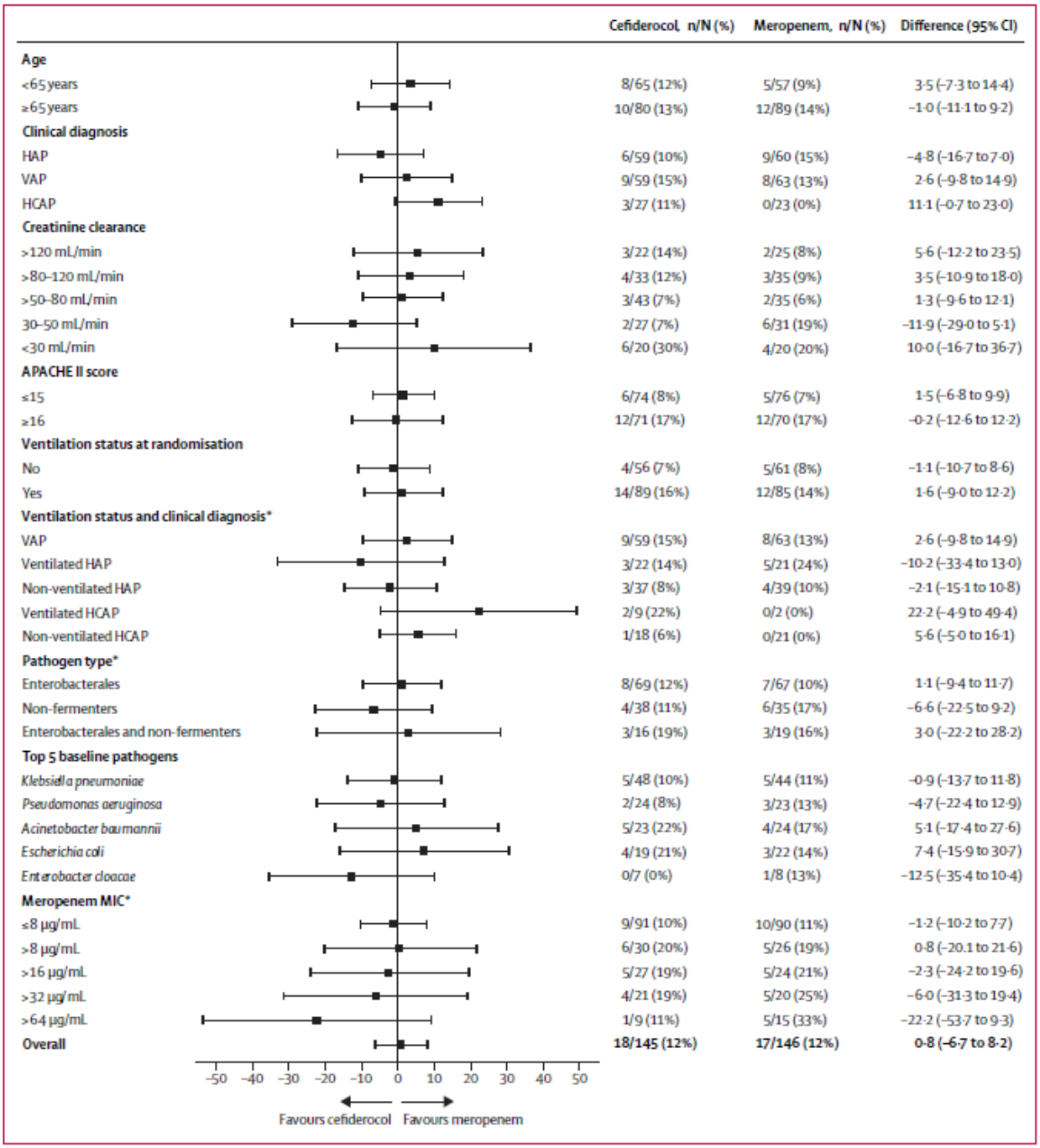


Figure 2: **All-cause mortality at day 14**

Data are shown for selected subgroups in the modified intention-to-treat population (appendix p 21). The widths of the 95% CIs for the subgroup analyses were not adjusted for multiplicity and therefore cannot be used to infer treatment effects. Percentages for overall and subgroup analyses were calculated as the number of patients who died from any cause at or before day 14 divided by the total number of patients in the analysis populations or within subgroups with known survival status at day 14. HAP=hospital-acquired pneumonia. VAP=ventilator-associated pneumonia. HCAP=health care-associated pneumonia. APACHE II=Acute Physiology and Chronic Health Evaluation II. MIC=minimum inhibitory concentration. *Post-hoc analysis categories.

Table 12. Secondary Endpoints, clinical cure and microbiological eradication at TOC in the mITT (from Wunderink et. al. (47))

	Cefiderocol (n=145)	Meropenem (n=147)	Treatment difference (95% CI)
Clinical cure			
All patients	94/145 (65%)	98/147 (67%)	-1·8 (-12·7 to 9·0)
HAP	33/59 (56%)	41/60 (68%)	-12·4 (-29·7 to 4·9)
VAP	39/59 (66%)	36/64 (56%)	9·9 (-7·3 to 27·0)
HCAP	22/27 (82%)	21/23 (91%)	-9·8 (-28·5 to 8·8)
Top five baseline pathogens			
Klebsiella pneumoniae	31/48 (65%)	29/44 (66%)	-1·3 (-20·8 to 18·1)
Pseudomonas aeruginosa	16/24 (67%)	17/24 (71%)	-4·2 (-30·4 to 22·0)
Acinetobacter baumannii	12/23 (52%)	14/24 (58%)	-6·2 (-34·5 to 22·2)
Escherichia coli	12/19 (63%)	13/22 (59%)	4·1 (-25·8 to 33·9)
Enterobacter cloacae	5/7 (71%)	4/8 (50%)	21·4 (NA)
Microbiological eradication			
All patients	59/145 (41%)	61/147 (42%)	-0·8 (-12·1 to 10·5)
HAP	21/59 (36%)	27/60 (45%)	-9·4 (-26·9 to 8·1)
VAP	25/59 (42%)	22/64 (34%)	8·0 (-9·2 to 25·2)
HCAP	13/27 (48%)	12/23 (52%)	-4·0 (-31·8 to 23·8)
Top five baseline pathogens			
K pneumoniae	21/48 (44%)	22/44 (50%)	-6·3 (-26·6 to 14·1)
P aeruginosa	9/24 (38%)	11/24 (46%)	-8·3 (-36·1 to 19·5)
A baumannii	9/23 (39%)	8/24 (33%)	5·8 (-21·7 to 33·2)
E coli	10/19 (53%)	11/22 (50%)	2·6 (-28·0 to 33·3)
E cloacae	4/7 (57%)	3/8 (38%)	19·6 (NA)

The modified intention-to-treat population included all randomly assigned patients who met inclusion criteria and received at least one dose of study drug, excluding patients with Gram-positive monomicrobial infections. Data are n/N (%) unless stated otherwise. The treatment difference (cefiderocol minus meropenem) is the estimate of the difference in clinical cure or microbiological eradication rate at test of cure between the two treatment groups. HAP=hospital-acquired pneumonia. VAP=ventilator-associated pneumonia. HCAP=health care-associated pneumonia. NA=not available.

Table 3: **Clinical cure and microbiological eradication at test of cure in the modified intention-to-treat population**

CREDIBLE-CR

CREDIBLE-CR was a small, randomized, open-label study conducted to evaluate efficacy of cefiderocol and best available therapy (BAT) in patients with confirmed CR infections. This study was designed as a descriptive study without hypothesis testing. No formal analysis was planned for any outcomes, and the analysis described below is descriptive. Patients with nosocomial pneumonia, BSI/sepsis, or cUTI were included in the study. Most of these patients had severe underlying conditions and ongoing infections for weeks prior to receiving cefiderocol. CREDIBLE-CR was designed to be observational, with no inferential analysis to detect differences between the treatment groups for any of the outcomes. A total of 101 patients received cefiderocol treatment. Cefiderocol demonstrated similar clinical and microbiological efficacy as BAT in this study (Table 13). Full results of this study have been published in *Lancet Infectious Diseases* (48).

Table 13. Clinical cure by Clinical Diagnosis and time point (from Bassetti et. al. (48))

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=40)	Best available therapy (n=19)	Cefiderocol (n=23)	Best available therapy (n=14)	Cefiderocol (n=17)	Best available therapy (n=5)	Cefiderocol (n=80)	Best available therapy (n=38)
Clinical outcomes								
End of treatment								
Clinical cure	24 (60%; 43·3–75·1)	12 (63%; 38·4–83·7)	16 (70%; 47·1–86·8)	7 (50%; 23·0–77·0)	13 (77%; 50·1–93·2)	3 (60%; 14·7–94·7)	53 (66%; 54·8–76·4)	22 (58%; 40·8–73·7)
Clinical failure	13 (33%)	7 (37%)	6 (26%)	7 (50%)	1 (6%)	1 (20%)	20 (25%)	15 (40%)
Indeterminate	3 (8%)	0	1 (4%)	0	3 (18%)	1 (20%)	7 (9%)	1 (3%)
Test of cure								
Clinical cure*	20 (50%; 33·8–66·2)	10 (53%; 28·9–75·6)	10 (43%; 23·2–65·5)	6 (43%; 17·7–71·1)	12 (71%; 44·0–89·7)	3 (60%; 14·7–94·7)	42 (53%; 41·0–63·8)	19 (50%; 33·4–66·6)
Clinical failure	16 (40%)	6 (32%)	9 (39%)	7 (50%)	2 (12%)	1 (20%)	27 (34%)	14 (37%)
Indeterminate	4 (10%)	3 (16%)	4 (17%)	1 (7%)	3 (18%)	1 (20%)	11 (14%)	5 (13%)
Follow-up								
Sustained clinical cure	20 (50%; 33·8–66·2)	6 (32%; 12·6–56·6)	9 (39%; 19·7–61·5)	4 (29%; 8·4–58·1)	9 (53%; 27·8–77·0)	3 (60%; 14·7–94·7)	38 (48%; 36·2–59·0)	13 (34%; 19·6–51·4)
Relapse	0	3 (16%)	1 (4%)	1 (7%)	1 (6%)	0	2 (3%)	4 (11%)
Clinical failure	16 (40%)	6 (32%)	9 (39%)	7 (50%)	2 (12%)	1 (20%)	27 (34%)	14 (37%)
Indeterminate	4 (10%)	4 (21%)	4 (17%)	2 (14%)	5 (29%)	1 (20%)	13† (16%)	7† (18%)
Microbiological outcomes								
End of treatment								
Eradication	12 (30%; 16·6–46·5)	5 (26%; 9·1–51·2)	14 (61%; 38·5–80·3)	4 (29%; 8·4–58·1)	12 (71%; 44·0–89·7)‡	1 (20%; 0·5–71·6)‡	38 (48%; 36·2–59·0)	10 (26%; 13·4–43·1)
Persistence	15 (38%)	9 (47%)	1 (4%)	1 (7%)	0	0	16 (20%)	10 (26%)
Indeterminate	13 (33%)	5 (26%)	8 (35%)	9 (64%)	5 (29%)	4 (80%)	26 (33%)	18 (47%)
Test of cure								
Eradication§	9 (23%; 10·8–38·5)	4 (21%; 6·1–45·6)	7 (30%; 13·2–52·9)	4 (29%; 8·4–58·1)	9 (53%; 27·8–77·0)‡	1 (20%; 0·5–71·6)‡	25 (31%; 21·3–42·6)	9 (24%; 11·4–40·2)
Persistence	8 (20%)	7 (37%)	3 (13%)	2 (14%)	5 (29%)	1 (20%)	16 (20%)	10 (26%)
Indeterminate	23 (58%)	8 (42%)	13 (57%)	8 (57%)	3 (18%)	3 (60%)	39 (49%)	19 (50%)
Follow-up								
Sustained eradication	8 (20%; 9·1–35·6)	3 (16%; 3·4–39·6)	6 (26%; 10·2–48·4)	3 (21%; 4·7–50·8)	7 (41%; 18·4–67·1)‡	1 (20%; 0·5–71·6)‡	21 (26%; 17·0–37·3)	7 (18%; 7·7–34·3)
Recurrence	0	1 (5%)	0	0	0	0	0	1 (3%)
Persistence	8 (20%)	7 (37%)	3 (13%)	2 (14%)	5 (29%)	1 (20%)	16 (20%)	10 (26%)
Indeterminate	24 (60%)	8 (42%)	14 (61%)	9 (64%)	5 (29%)	3 (60%)	43¶ (54%)	20¶ (53%)

Data are n (%) or n (%, 95% CI), categorised by clinical diagnosis and visit. *Primary endpoint for patients with nosocomial pneumonia, or bloodstream infections or sepsis. †Indeterminate clinical responses were reported as either deaths (for seven patients assigned cefiderocol and three assigned best available therapy), or missing (for six patients assigned cefiderocol and four assigned best available therapy [definitions in the appendix, p 8]). ‡Eradication was defined as reduction of urine culture Gram-negative uropathogens from at least 10^5 colony forming units (CFU) per mL at baseline to less than 10^3 CFU per mL. §Primary endpoint for patients with complicated urinary tract infections. ¶Indeterminate microbiological responses were reported as deaths (21 patients assigned cefiderocol and six assigned best available therapy); additional therapy required (for ten patients assigned cefiderocol and seven assigned best available therapy); or missing (for 12 patients assigned cefiderocol and seven assigned best available therapy [definitions in the appendix, p 10]).

Table 3: Clinical and microbiological secondary outcomes in the carbapenem-resistant microbiological intention-to-treat population

The mean age of patients included in this study was 63.1 and 63.0, for cefiderocol and BAT groups, respectively, though the median age of cefiderocol patients was higher at 69 years versus 62 years in the BAT group. The mean APACHE II score was 15.3 and 15.4 for cefiderocol and BAT groups, respectively. Most patients receiving cefiderocol were on monotherapy, while most BAT patients received combination therapy; 66% of the BAT regimens included colistin. In post-hoc analyses in the safety

population, patients in the BAT group received rescue therapy more frequently than those in the cefiderocol group.

Mortality was assessed during this study, and a mortality imbalance was observed, with numerically more deaths in the cefiderocol group than the BAT group for patients with pneumonia or BSI, but not cUTI (Table 14).

While regression analysis did not identify a baseline variable that explained the mortality findings in CREDIBLE-CR, the mortality imbalance appeared to be driven by *Acinetobacter* spp. infections. In subjects with *Acinetobacter* spp. infection and a history of shock (both shock at baseline and a history of shock within 31 days of baseline), mortality rates were much higher than in subjects without a history of shock in both treatment groups (61). The proportion of subjects with a history of shock, or who were in an ICU at admission, was higher for the cefiderocol group than for the BAT group in subjects with *Acinetobacter* spp. infection. These factors imply a higher risk of mortality, and so may provide an explanation for some of the difference in mortality rates between the treatment groups in the CREDIBLE-CR study.

Whereas the mortality rate in the cefiderocol group was consistent with previous studies in similar populations with high levels of *A. baumannii* infections (62-64), the mortality rate in the BAT group was substantially lower than expected from previous studies (62-70). The reason for the lower than expected mortality in the BAT group is not clear but is likely also due to a variety of factors related to baseline imbalances and other anomalies (such as the low mortality associated with high APACHE II and SOFA scores). The evidence suggests that the mortality rate in the BAT group was unexpectedly low for the population randomized and that the mortality in the cefiderocol group was consistent with what has been reported in previous studies.

Table 14: All-cause mortality in the safety population (from Bassetti et. al. (48))

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=45)	Best available therapy (n=22)	Cefiderocol (n=30)	Best available therapy (n=17)	Cefiderocol (n=26)	Best available therapy (n=10)	Cefiderocol (n=101)	Best available therapy (n=49)
Day 14	11 (24%; 12·9—39·5)	3 (14%; 2·9-34·9)	5 (17%; 5·6-34·7)	1 (6%; 0·1-28·7)	3 (12%; 2·4-30·2)	2 (20%; 2·5-55·6)	19 (19%; 11·7-27·8)	6 (12%; 4·6-24·8)
Day 28	14 (31%; 18·2-46·6)	4 (18%; 5·2-40·3)	7 (23%; 9·9-42·3)	3 (18%; 3·8-43·4)	4 (15%; 4·4-34·9)	2 (20%; 2·5-55·6)	25 (25%; 16·7-34·3)	9 (18%; 8·8-32·0)
End of study	19 (42%; 27·7-57·8)	4 (18%; 5·2-40·3)	11 (37%; 19·9-56·1)	3 (18%; 3·8-43·4)	4 (15%; 4·4-34·9)	2 (20%; 2·5-55·6)	34 (34%; 24·6-43·8)	9 (18%; 8·8-32·0)

Data are n (%; 95% CI) by clinical diagnosis and overall. Percentages were calculated using n as the denominator, where n was the number of patients in the safety population who had the specified clinical diagnosis and known vital status at each timepoint.

Table 5: All-cause mortality in the safety population

Compassionate Use and Expanded Access Programs

Since the start of the compassionate use program in 2016, approximately 300 requests have been received and 184 cases have been granted supply. Patients were included from 12 countries and ranged in age from 5 months to 84 years. The compassionate use program was suspended in the US post-

approval and commercial launch of the drug on February 24, 2020. Details on the compassionate use program can be found on Clinicaltrials.gov under NCT03780140.

Cefiderocol is still supplied through the compassionate use programs in Europe, the Asia Pacific region and Canada (Special Access Programme) for qualified patients who have limited treatment options and are not eligible for a clinical trial. The criteria for compassionate use of cefiderocol are highly restrictive. It required a life-threatening infection with no alternative treatment options available. If the infection was sensitive to colistin, compassionate use of cefiderocol was not granted unless colistin was contraindicated. If established colistin toxicity requiring discontinuation occurred, the patient was considered eligible for compassionate use.

Over 60% of the patients receiving cefiderocol survived when no other possible treatment options were available to them (69). None of the observed deaths were considered to be related to cefiderocol (71). Of those who have completed therapy under the compassionate use program, nine positive outcomes are published to date (72-80). Cefiderocol has demonstrated a manageable safety profile with the longest use being more than 90 days in a renal transplant patient where no apparent safety issues were observed (69).

Shionogi has also supplied cefiderocol to patients in Europe under an Early Access Program. As of October 2020, 132 patients have been treated under the program, including many with bacterial infections secondary to COVID-19. Most recently, Falcone *et. al*. published an interesting case series of COVID-19 and burn patients, all ventilated and with carbapenem-resistant infections of *A. baumannii* or other CR Gram-negative bacteria. These patients had a median APACHE-II score of 37.5 and had been hospitalized for a median of 23 days prior to infection. All patients were treated with cefiderocol and after 30 days there was a 90% survival rate with 70% of patients experiencing clinical success (81).

10. Review of harms and toxicity: summary of evidence of safety

Estimate of total patient exposure to date

As of 21 February 2020, 771 subjects have received cefiderocol in clinical studies; this includes 212 healthy subjects (including subjects with renal impairment who were otherwise healthy) in clinical pharmacology studies, 300 subjects in the APEKS-cUTI study, 148 subjects in the APEKS-NP study, 101 subjects in the CREDIBLE-CR study and 7 subjects in the Phase 1 ELF study. More than 300 patients have received treatment with cefiderocol under compassionate use and expanded access programs. In addition, the following studies are on-going or planned (Table 15):

Table 15. Summary of on-going or planned human studies

Type of Study (Identifier)	Objectives of the Study	Subject Population	Duration of Treatment	Study Status
Phase 2 pediatric study1-US (1704R2133)	Evaluate safety, tolerability, and PK	Part 1: pediatric subjects 3 months to < 18 years of age with Gram-negative bacterial infection Part 2: pediatric subjects 3 months to < 18 years of age with cUTI	Up to 14 days	Ongoing

		78 to 85 planned subjects, 4:1 randomization		
Phase 2 pediatric study1-EU (1802R2135)	Evaluate safety, tolerability, and PK	54 planned pediatric subjects 3 months to < 18 years of age with Gram-negative bacterial infection	Up to 14 days	Ongoing
Phase 2 pediatric study 2 (TBD)	Evaluate safety, tolerability, and PK	16 planned pediatric subjects with less than 3 months of age Gram-negative bacterial infection	Up to 14 days	Planned
Phase 2 BSI study (GAME CHANGER)	Evaluate safety and efficacy	284 planned adult subjects with bloodstream infections (BSI) caused by Gram-negative pathogens	5-14 days	Ongoing

Cefiderocol is commercially available in the US, UK and Germany; launch in other European countries is expected in 2021. Cefiderocol was launched in the UK launch was on September 15, 2020, with the brand name FETCROJA. It launched in the US on February 24, 2020, with the brand name FETROJA.

Description of the adverse effects/reactions and estimates of their frequency

In total across the APEKS-cUTI, APEKS-NP, and CREDIBLE studies, 386 SAEs were reported: 226 SAEs in subjects who had been treated with cefiderocol, 103 SAEs in subjects who had been treated with meropenem, 17 SAEs in subjects who had been treated with IPM/CS, and 40 SAEs in subjects who had been treated with BAT. Table 16 summarizes treatment related adverse events (AEs) for each trial and for the total patient population studied. In the total sample, 56/549 (10.2%) patients treated with cefiderocol experienced treatment related AEs and 45/347 (13.0%) patients treated with comparators experienced treatment related AEs. Overall, there were less treatment emergent AEs with cefiderocol (344/549 [67.1%]) vs comparators (252/347 [72.6%]). The most common adverse reactions for cefiderocol were diarrhea (8.2%), constipation (4.6%), pyrexia (4.0%) and UTI (4.7%).

A serious adverse reaction (SAR) is a SAE that is determined by the investigator to have a reasonable possibility of having been caused by the study medication. In total, 22 SARs were reported: 8 SARs in patients who had been treated with cefiderocol, 6 SARs in patients who had been treated with meropenem, 1 SAR in patients who had been treated with IPM/CS, and 7 SARs in patients treated with BAT.

Table 16. Patients with Treatment Related Adverse Events by System Organ Class and Preferred Term (All Phase II/III Studies) Safety Population

	APEKS-cUTI		**CREDIBLE-CR Study**		**APEKS NP Study**		**All Studies**	
System Organ Class - Preferred Term	Cefiderocol N=300 n (%)	Imipenem/ Cilastatin N=148 n (%)	Cefiderocol N=101 n (%)	BAT N=49 n (%)	Cefiderocol N=148 n (%)	Meropenem N=150 n (%)	Cefiderocol N=549 n (%)	Comparator N=347 n (%)
Subjects with any Treatment Related AEs	27 (9.0)	17 (11.5)	15 (14.9)	11 (22.4)	14 (9.5)	17 (11.3)	56 (10.2)	45 (13.0)
Blood and lymphatic system disorders	0	0	0	0	0	2 (1.3)	0	2 (0.6)
- Disseminated intravascular coagulation	0	0	0	0	0	1 (0.7)	0	1 (0.3)
- Thrombocytopenia	0	0	0	0	0	1 (0.7)	0	1 (0.3)
Cardiac disorders	0	1 (0.7)	0	0	0	0	0	1 (0.3)
- Tachycardia	0	1 (0.7)	0	0	0	0	0	1 (0.3)
Ear and labyrinth	0	0	0	0	1 (0.7)	0	1 (0.2)	0

disorders								
- Ear discomfort	0	0	0	0	1 (0.7)	0	1 (0.2)	0
Gastrointestinal disorders	9 (3.0)	5 (3.4)	4 (4.0)	1 (2.0)	3 (2.0)	5 (3.3)	16 (2.9)	11 (3.2)
- Diarrhoea	4 (1.3)	3 (2.0)	2 (2.0)	0	3 (2.0)	5 (3.3)	9 (1.6)	8 (2.3)
- Nausea	3 (1.0)	1 (0.7)	0	0	0	0	3 (0.5)	1 (0.3)
- Vomiting	1 (0.3)	1 (0.7)	0	1 (2.0)	0	0	1 (0.2)	2 (0.6)
- Abdominal pain upper	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Ascites	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Constipation	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Dry mouth	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Stomatitis	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Upper gastrointestinal haemorrhage	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Lipoedema	0	1 (0.7)	0	0	0	0	0	1 (0.3)
General disorders and administration site conditions	5 (1.7)	0	2 (2.0)	0	0	2 (1.3)	7 (1.3)	2 (0.6)
- Oedema peripheral	2 (0.7)	0	0	0	0	0	2 (0.4)	0
- Infusion site pain	2 (0.7)	0	0	0	0	0	2 (0.4)	0
- Feeling hot	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Oedema	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Pyrexia	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Infusion site erythema	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Hyperthermia	0	0	0	0	0	1 (0.7)	0	1 (0.3)
- Multiple organ dysfunction syndrome	0	0	0	0	0	1 (0.7)	0	1 (0.3)
Hepatobiliary disorders	0	1 (0.7)	0	0	1 (0.7)	1 (0.7)	1 (0.2)	2 (0.6)
- Hepatic failure	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Hepatic function abnormal	0	1 (0.7)	0	0	0	0	0	1 (0.3)
- Hepatocellular injury	0	0	0	0	0	1 (0.7)	0	1 (0.3)
Immune system disorders	1 (0.3)	0	0	1 (2.0)	0	0	1 (0.2)	1 (0.3)
- Drug hypersensitivity	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Anaphylactic reaction	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Infections and infestations	4 (1.3)	6 (4.1)	2 (2.0)	2 (4.1)	3 (2.0)	6 (4.0)	9 (1.6)	14 (4.0)
- Clostridium difficile colitis	1 (0.3)	4 (2.7)	1 (1.0)	0	0	0	2 (0.4)	4 (1.2)
- Oral candidiasis	1 (0.3)	0	0	0	1 (0.7)	0	2 (0.4)	0
- Candiduria	2 (0.7)	0	0	0	0	0	2 (0.4)	0
- Clostridium difficile infection	0	0	0	0	1 (0.7)	2 (1.3)	1 (0.2)	2 (0.6)
- Pseudomembranous colitis	0	0	1 (1.0)	1 (2.0)	0	0	1 (0.2)	1 (0.3)
- Sepsis	0	0	0	1 (2.0)	1 (0.7)	0	1 (0.2)	1 (0.3)
- Fungal infection	0	1 (0.7)	0	0	0	0	0	1 (0.3)
- Septic shock	0	0	0	1 (2.0)	0	0	0	1 (0.3)
- Systemic candida	0	0	0	0	0	1 (0.7)	0	1 (0.3)
- Vaginal infection	0	1 (0.7)	0	0	0	0	0	1 (0.3)
- Urinary tract infection fungal	0	0	0	0	0	1 (0.7)	0	1 (0.3)
- Pseudomonas infection	0	0	0	0	0	1 (0.7)	0	1 (0.3)
- Candida infection	0	0	0	0	0	1 (0.7)	0	1 (0.3)
Investigations	5 (1.7)	2 (1.4)	8 (7.9)	2 (4.1)	4 (2.7)	4 (2.7)	17 (3.1)	8 (2.3)
- Alanine aminotransferase increased	1 (0.3)	0	3 (3.0)	0	2 (1.4)	1 (0.7)	6 (1.1)	1 (0.3)
- Gamma-glutamyltransferase increased	4 (1.3)	1 (0.7)	0	0	2 (1.4)	0	6 (1.1)	1 (0.3)
- Aspartate aminotransferase increased	0	0	3 (3.0)	0	2 (1.4)	1 (0.7)	5 (0.9)	1 (0.3)
- Transaminases increased	0	0	1 (1.0)	0	1 (0.7)	0	2 (0.4)	0
- Liver function test	0	0	2 (2.0)	0	0	0	2 (0.4)	0

increased								
- Hepatic enzyme increased	1 (0.3)	0	0	1 (2.0)	0	2 (1.3)	1 (0.2)	3 (0.9)
- Blood creatinine increased	0	1 (0.7)	1 (1.0)	0	0	0	1 (0.2)	1 (0.3)
- Blood pressure increased	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Blood creatine increased	0	0	0	1 (2.0)	0	0	0	1 (0.3)
- Blood alkaline phosphatase increased	0	1 (0.7)	0	0	0	0	0	1 (0.3)
Metabolism and nutrition disorders	0	0	1 (1.0)	1 (2.0)	0	0	1 (0.2)	1 (0.3)
- Hypokalaemia	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Metabolic acidosis	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Myalgia	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Nervous system disorders	1 (0.3)	4 (2.7)	1 (1.0)	1 (2.0)	3 (2.0)	0	5 (0.9)	5 (1.4)
- Dysgeusia	1 (0.3)	1 (0.7)	1 (1.0)	0	0	0	2 (0.4)	1 (0.3)
- Headache	0	3 (2.0)	0	0	1 (0.7)	0	1 (0.2)	3 (0.9)
- Dizziness	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Paraesthesia	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Status epilepticus	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Psychiatric disorders	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Confusional state	0	0	0	0	1 (0.7)	0	1 (0.2)	0
Renal and urinary disorders	0	0	0	5 (10.2)	0	0	0	5 (1.4)
- Acute kidney injury	0	0	0	4 (8.2)	0	0	0	4 (1.2)
- Renal disorder	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Reproductive system and breast disorders	0	0	0	0	0	1 (0.7)	0	1 (0.3)
- Vulvovaginal pruritus	0	0	0	0	0	1 (0.7)	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.0)	1 (2.0)	2 (1.4)	0	3 (0.5)	1 (0.3)
- Pleural effusion	0	0	1 (1.0)	0	1 (0.7)	0	2 (0.4)	0
- Acute respiratory failure	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Asthma	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Respiratory arrest	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	3 (1.0)	0	2 (2.0)	0	2 (1.4)	1 (0.7)	7 (1.3)	1 (0.3)
- Rash	0	0	1 (1.0)	0	1 (0.7)	0	2 (0.4)	0
- Pruritus	1 (0.3)	0	0	0	0	1 (0.7)	1 (0.2)	1 (0.3)
- Drug eruption	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Erythema	1 (0.3)	0	0	0	0	0	1 (0.2)	0
- Palmar erythema	0	0	0	0	1 (0.7)	0	1 (0.2)	0
- Rash maculo-papular	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Vascular disorders	0	0	1 (1.0)	0	0	0	1 (0.2)	0
- Hypertension	0	0	1 (1.0)	0	0	0	1 (0.2)	0

Summary of available data (appraisal of quality, summary of results) and summary of comparative safety against comparators

Overall, cefiderocol was generally well tolerated, and its safety profile was found to be consistent with that of other cephalosporin antibacterials. The clinical safety for cefiderocol has been investigated in three randomized clinical trials, two specific to different infection sites and one specific to CR pathogens. Five hundred and forty-nine patients were treated with cefiderocol in these trails.

cUTI study (APEKS-cUTI): The proportion of patients who experienced at least one adverse event (AE) was lower in the cefiderocol group than in the IPM/CS group (41 % vs 51%). Gastrointestinal disorders, such as diarrhea and constipation, were the most common adverse events and there was an increased incidence of *C. difficile* colitis in the imipenem/cilastatin arm compared with cefiderocol. Serious adverse events (SAE) occurred in a numerically lower proportion of cefiderocol-treated patients than of IPM/CS-treated patients (5% vs 8%). The most frequently observed AEs were gastrointestinal, such as diarrhea, experienced by 4.3% (13/300) and 6.1% (9/148) of cefiderocol- and IPM/CS-treated subjects, respectively.

HABP/VABP/HCABP study (APEKS-NP): Overall, treatment emergent adverse events (TEAEs) and treatment-related AEs were balanced between treatment arms. Serious adverse events occurred in 36% of patients treated with cefiderocol and 30% of patients treated with meropenem. The most frequently observed AE was urinary tract infection (15.5% in cefiderocol group and 10.7% in meropenem group), hypokalemia (10.8% in cefiderocol group and 15.3% in meropenem group) and anemia (8.1% in cefiderocol group and 8% in meropenem group).

CR study (CREDIBLE-CR): The cefiderocol group had a lower incidence of AEs and treatment-related AEs, but a higher incidence of death, SAEs, and discontinuation due to AEs, compared with BAT. The incidence of treatment-related AEs leading to discontinuation was similar between treatment groups. An imbalance in mortality was observed in the cefiderocol arm compared to BAT (18/49 vs 5/25). Through assessment by the investigator and two independent committees (one blinded), no deaths were found to be causally associated with cefiderocol. Furthermore, whereas the mortality rate in the cefiderocol group was consistent with previous studies in similar populations, the evidence suggests that the mortality rate in the BAT group was unexpectedly low for the randomized population. No single factor that would explain the imbalance was identified. Small patient numbers and multiple confounders preclude definitive conclusions.

Like in any other β-lactam antibacterial, patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibacterial medicinal products may also be hypersensitive to cefiderocol. Before initiating therapy with cefiderocol, careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibacterials.

11. Summary of available data on comparative cost and cost-effectiveness

Cefiderocol is appropriate for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. Treatment options may be limited due to MDR or CR pathogens, which are associated with higher mortality rates and increased clinical and economic burden. For critically ill patients at risk of rapid deterioration, where a MDR or CR pathogen is suspected, cefiderocol can provide broad efficacy requiring no trade-off against possible toxicity. Without definitive evidence that an infection is resistant to first-line treatment, empiric therapy may be used and appropriate treatment may be delayed.

A recent systematic review in *Chest* examined the impact of delayed antibiotic therapy in patients with severe bacterial infections. The authors found that mortality was significantly lower in patients who did not experience delay in receiving the appropriate therapy (82). In addition, several systematic reviews

examined the impact of AMR and MDR infections on healthcare costs, and all found an association of increased costs with resistance (83-85). As a result, antibiotics that can effectively treat MDR infections, like cefiderocol, have the potential to impart both health benefits and healthcare savings.

The wholesale acquisition cost of cefiderocol in the UK and US is shown in Table 17.

Table 17: Cefiderocol availability and pricing

Country	Pack size	Currency	Price to wholesaler
United Kingdom	10 vials	GBP	£ 1,319.00
United States	10 vials	USD	$ 1,833.33

The treatment length varies from patient to patient, depending on infection site and underlying patient conditions; the dose of cefiderocol varies with renal function, but for a normal renal function, the standard dose is 2g on a 3h infusion, every 8h. This represents a daily dose of 6 vials a day, which is equivalent to:

- £ 791.4 per day in the UK
- $ 1,099.99 per day in the US

The US Centers for Medicare and Medicaid Services has assigned a maximum payment of $7,919.86 per patient administered cefiderocol, which includes the New Technology Add-On Payment (86).

An analysis of cost effectiveness was performed comparing cefiderocol to colistin-based regimens for the treatment of cUTI and HABP/VABP caused by confirmed CR pathogens (87). This analysis found cefiderocol to be a cost-effective option for cUTI and HABP/VABP against the comparators. A decision-tree model was created to determine the cost-effectiveness of cefiderocol versus colistin-based regimens for the treatment of CR cUTI and CR nosocomial pneumonia infections in the US. A deterministic sensitivity analysis (DSA) was conducted that varied both benefits and costs, and a probabilistic sensitivity analysis (PSA) was based on 5000 simulations. These analyses showed that cefiderocol was cost-effective versus colistin-based regimens with an ICER: $14,616/QALY; $8,683 incremental costs and 0.59 incremental QALY (87).

12. Summary of regulatory status and market availability of the medicine

Cefiderocol has been approved for use in both the US and Europe, and regulatory details are included in Table 18.

Table 18. Regulatory status of the technology

Organization issuing approval	Verbatim wording of the (expected) indication(s)	Date of approval	Launch Status
FDA	FETROJA® is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused	November 14, 2019	Launched in the US on February 24, 2020

	by the following susceptible Gram-negative microorganisms: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Enterobacter cloacae complex		
	FETROJA is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens	September 27, 2020	
EMA	Fetcroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options	April 23, 2020	Launched in the UK on September 15, 2020; launched in Germany on November 23, 2020*

* Reimbursement and HTA assessments are in process in other EU markets; launch will occur when reimbursement is secured. Early access programs are in place for patients who may need access in the interim.

13. Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia)

Cefiderocol is not currently available in any pharmacopoeia standards.

14. Comprehensive reference list

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Appendix A

To identify all relevant studies for cefiderocol and comparators, a comprehensive systematic literature review was conducted comprising *in vitro* and *in-vivo* studies, as well as any comparative or non-comparative studies and RCTs (including cross-over RCTs). The literature search was conducted in the databases and information resources shown in Table 1. The same databases and information sources were searched for the most recent search update in September 2020.

Table 1. Databases and information sources searched

Database / information source	Interface / URL	Coverage
MEDLINE ALL	Ovid SP	Biomedical journal literature
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/	Biomedical journal literature
Embase	OvidSP	Biomedical journal literature
Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Cochrane Library	Randomized and quasi-randomized controlled trials
Cochrane Database of Systematic Reviews	Wiley Cochrane Library	Systematic reviews
Database of Abstracts of Reviews of Effects (DARE)	CRD website	Systematic reviews
Health Technology Assessment (HTA)	CRD website	Health technology assessment
Web of Science	http://apps.webofknowledge.com/	Science, social science, arts, humanities
BIOSIS Citation Index	http://apps.webofknowledge.com/	Life sciences and biomedical research
ClinicalTrials.gov	https://www.clinicaltrials.gov/ct	Records for registered clinical studies
WHO International Clinical Trials Registry Platform (WHO ICTRP)	http://www.who.int/ictrp/en/	Trial registration data sets

Recent research published as conference abstracts were identified by searching Embase (which indexes a significant number of conference publications). In addition, where the following conferences (identified as highly relevant by the research team) were not indexed in Embase from 2016 to 2019, we conducted hand-searches for abstracts via conference webpages:

- European Congress of Clinical Microbiology & Infectious Diseases (ECCMID)
- IDWeek
- European Respiratory Society (ERS) International Congress

We also checked the reference lists of any relevant reviews or systematic reviews for eligible records. Three hundred sixteen (316) records were assessed for relevance. 49 records were excluded after an

assessment of the information in the title and abstract. 267 full text documents were assessed, and 153 records were included (Table 2). The initial review included publications through April 2020 and additional records were added through September 2020. Records were excluded if they were a review, an opinion piece, or systematic review for reference checking; had an ineligible study design, intervention, or outcomes; or were unobtainable.

Table 2. Studies identified in a systematic literature review through September 2020. Studies are characterized into the following categories: In vitro, In vitro assessment of specific clinical samples, In vivo, Clinical, Mixed categories, Modeling, Systematic review protocol.

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In vitro
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